(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 513 387 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
01.03.2000 Bulletin 2000/09

(21) Application number: **91920815.7**

(22) Date of filing: **29.11.1991**

(51) Int. Cl.[7]: **C07D 263/32**, C07D 263/34, C07D 263/52, C07D 263/56, C07D 263/57, C07D 263/58, C07D 277/24, C07D 417/04, C07D 277/30

(86) International application number:
PCT/JP91/01659

(87) International publication number:
WO 92/09586 (11.06.1992 Gazette 1992/13)

(54) THIAZOLE DERIVATIVES AS ACTIVE OXYGEN INHIBITORS

THIAZOLEDERIVATE ALS INHIBITOREN VON AKTIVEM SAUERSTOFF

DERIVES DE THIAZOLE COMME INHIBITEURS D'OXYGENE ACTIF

(84) Designated Contracting States:
CH DE DK ES FR GB IT LI NL SE

(30) Priority: **30.11.1990 JP 33772790**

(43) Date of publication of application:
19.11.1992 Bulletin 1992/47

(60) Divisional application:
99107493.1 / 0 934 937

(73) Proprietor:
OTSUKA PHARMACEUTICAL CO., LTD.
Chiyoda-ku, Tokyo 101-0048 (JP)

(72) Inventors:
- **CHIHIRO, Masatoshi**
  Naruto-shi, Tokushima 772 (JP)
- **KOMATSU, Hajime**
  Koto-ku, Tokyo (JP)
- **TOMINAGA, Michiaki**
  Itano-gun, Tokushima 771-13 (JP)
- **YABUUCHI, Yoichi**
  Tokushima-shi, Tokushima 771-01 (JP)

(74) Representative:
Hansen, Bernd, Dr. Dipl.-Chem. et al
Hoffmann Eitle,
Patent- und Rechtsanwälte,
Postfach 81 04 20
81904 München (DE)

(56) References cited:

EP-A- 0 037 274	**FR-M- 8 018**
JP-A- 1 022 861	**JP-A- 1 113 367**
JP-A- 48 049 757	**JP-A- 50 111 067**
JP-A- 56 123 544	**JP-A- 58 120 257**
JP-A- 58 201 771	**JP-A- 58 219 169**
JP-A- 60 051 111	**JP-A- 61 040 276**
JP-B- 39 010 130	**JP-B- 46 015 935**
JP-B- 46 024 696	**JP-B- 46 037 822**
JP-B- 46 039 856	**JP-B- 46 041 542**
JP-B- 46 043 776	**JP-B- 49 038 267**
JP-B- 49 038 268	**JP-B- 49 039 262**
JP-B- 50 003 315	**JP-B- 50 030 619**
JP-B- 61 023 790	**US-A- 1 970 656**
US-A- 3 462 448	

- **Decision Making in Drug Design (1983) pages 173-188**

EP 0 513 387 B1

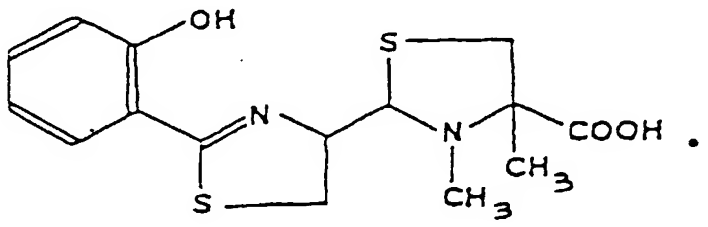
Description

Technical Field

[0001] The present invention relates to a superoxide radical inhibitor containing an azole derivative as the effective ingredient.

Background Art

[0002] It is thought that neutrophilic leukocytes show a germicidal activity to foreign invaders in living bodies by a wondering reaction, a feeding action, generation of superoxide radical (O_2^-) and release of lysosomal enzyme and play an important role in protection of living body. While neutrophilic leukocytes have the above reaction for living body protection, it has been made clear that the superoxide radical released by tissues or neutrophilic leukocytes during ischemia of tissues and subsequent blood re-perfusion or during acute inflammation at early stage destroys cells, causing functional disturbances of tissues [B.R. Lucchesi: Annual Review of Pharmacology and Toxicology, Vol. 26, p. 201 (1986); B.A. Freeman et al.: Laboratory Investigation, Vol. 47, p. 412 (1982); E. Braunwald, R.A. Kloner: Journal of Clinical Investigation, Vol. 76, p. 1713 (1985); J.L. Romson et al.: Circulation, Vol. 67, p. 1016 (1983)]. JP-A-1-22861 discloses that the following compound has anti-tumor and superoxide-removing activities

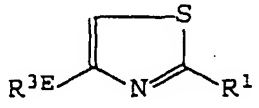


Disclosure of the Invention

[0003] Based on the thought that the major cause for the above-mentioned disturbances in cells, in particular the disturbances after ischemia and re-perfusion in heart, brain, kidney, lung and digestive tract lies in the superoxide radical released by neutrophilic leukocytes, the present invention has an object of providing a new drug for inhibiting the release of the superoxide radical.

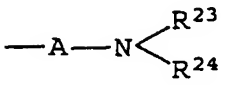
[0004] The present inventors made study for the above object and, as a result, found that certain azole derivatives show a very strong inhibitory activity for release of superoxide radical in living bodies. Further study based on the finding has led to the completion of the present invention.

[0005] According to a first aspect, the present invention provides a thiazole derivative of the general formula (1)

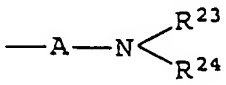


(1)

wherein R^1 represents a phenyl group which may have 1-3 alkoxy groups as substituents; and R^{3E} represents either (i) a pyridyl group optionally substituted by 1 to 3 substituents selected from an alkyl group, a benzoyl group, a C_1-C_6 alkanoyl group, a hydroxy group, a carboxy group, a C_1-C_6 alkoxycarbonyl group, a C_1-C_6 alkylthio group, a group of the formula:



(wherein A is a C_1-C_6 alkylene group or a group -C(=O)-; and R^{23} and R^{24}, which may be the same or different, each represent a hydrogen atom or a C_1-C_6 alkyl group; further R^{23} and R^{24} as well as the adjacent nitrogen atom being bonded thereto, together with or without another nitrogen atom or oxygen atom may form a five- to six-membered saturated heterocyclic group; and said five- to six-membered heterocyclic group may have a C_1-C_6 alkyl group as a substituent), a cyano group, a C_1-C_6 alkyl group having hydroxy groups, a phenylaminothiocarbonyl group and an amino C_1-C_6 alkoxycarbonyl group which may have a C_1-C_6 alkyl group as a substituent; or (ii) a furyl group which has 1 to 3 substituents selected from an alkyl group, a benzoyl group, a C_1-C_6 alkanoyl group, a hydroxy group, a carboxy group, a C_1-C_6 alkoxycarbonyl group, a C_1-C_6 alkylthio group, a group of the formula:



(wherein A, R^{23} and R^{24} are as defined above); a cyano group, a C_1-C_6 alkyl group having hydroxy groups, a phenylaminothiocarbonyl group and an amino C_1-C_6 alkoxycarbonyl group which may have a C_1-C_6 alkyl group as a substituent, or a salt thereof.

[0006] It is preferred that the group R^{3E} is a pyridyl group which may have 1 to 3 substituents selected from the group consisting of a carboxy group, a hydroxy group, a C_1-C_6 alkoxycarbonyl group and a C_1-C_6 alkyl group having hydroxy groups; or a salt thereof. More preferably, the substituents are selected from a carboxy group or a C_1-C_6 alkoxycarbonyl group.

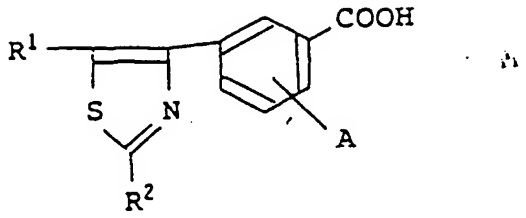
[0007] Alternatively, it is preferred that the substituent R^{3E} is a furyl group which has 1 to 3 substituents selected from the group consisting of a carboxy group, a hydroxy group, a C_1-C_6 alkoxycarbonyl group and a C_1-C_6 alkyl group having hydroxy groups; or a salt thereof.

[0008] In a preferred aspect, the present invention provides a superoxide radical inhibitor comprising the above thiazole derivative or salt thereof together with a pharmaceutically acceptable carrier.

[0009] Furthermore, the present invention provides the use of the above thiazole derivative for the manufacture of a medicament for the treatment of ulcers of the digestive tract, ischemic heart disease, cerebrovascular disease, microcirculation failure, Bechet disease, dermatovascular inflammation, ulcerative colitis, malignant rheumatoid arthritis, artheriosclerosis or diabetes mellitus, or for use as a hepatic or renal function improver.

[0010] The compounds of the present invention have an activity of inhibiting the release of superoxide radical from neutrophilic leukocytes or of removing the superoxide radical. Accordingly, they have an action of preventing or lowering the in vivo production of peroxidized lipids. Hence, the compounds are useful as an agent for preventing and treating various disturbances and diseases caused by excessive generation of superoxide radical, in vivo accumulation of peroxidized lipids, or defect of protective organizations therefor. More specifically, the drugs of the present invention are useful in a pharmaceutical field as a drug for protecting various tissue cells from disturbances associated with ischemia and blood re-perfusion, for example, a remedy for ulcers of the digestive tract (e.g. stress ulcer), a remedy for ischemic heart disease (e.g. myocardial infarction, arrhythmia), a remedy for cerebrovascular diseases (e.g. cerebral hemorrhage, cerebral infarction, temporal cerebral ischemic attack), and a hepatic and renal function improver for disturbances caused by transplant, microcirculation failure, etc., or as an agent for inhibiting various cell function disturbances believed to be caused by the superoxide radical abnormally generated by factors other than ischemia, for example, a remedy for Bechcet disease, dermatovascular inflammation, ulcerative colitis, malignant rheumatoid, arthritis, arteriosclerosis, diabetes mellitus, etc.

[0011] It is described in Japanese Patent Publication No. 15935/1971 that the compounds represented by the following general formula,



(wherein R^1 is a group selected from the group consisting of a hydrogen atom and a straight-chain or branched-chain lower alkyl group of 1 to 5 carbon atoms; R^2 is a group selected from the group consisting of a lower alkyl group having 1 to 5 carbon atoms, a phenylalkyl group which may be substituted with a lower alkyl or lower alkoxy group having 1 to 5 carbon atoms, or substituted with one or more halogen atoms, and a phenyl group; and A is a group selected from the group consisting of a hydrogen atom, a halogen atom, a hydroxyl group and a lower alkyl or lower alkoxy group having 1 to 5 carbon atoms.) have properties which are advantageous for fibrinolysis, platelet stickiness, ulcers and immunological treatments and can be used for prevention and treatment of thrombosis, arteriosclerosis, gastric ulcer and hypersecretion. The compounds of the present invention exhibit very strong inhibitory activities for releasing superoxide radical, even though as compared with the most similar compounds.

Best Mode for Carrying out the Invention

[0012] Each group shown in the present specification is specifically as follows.

[0013] The alkoxy group can be exemplified by straight-chain or branched-chain alkoxy groups having 1 to 18 carbon atoms such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentyloxy, hexyloxy, heptyloxy, octyloxy, nonyloxy, decyloxy, undecyloxy, dodecyloxy, tridecyloxy, tetradecyloxy, pentadecyloxy, hexadecyloxy, heptadecyloxy, octadecyloxy.

[0014] The lower alkyl group can be exemplified by straight-chain or branched-chain alkyl groups having 1 to 6 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, hexyl.

[0015] The lower alkylthio group can be exemplified by straight-chain or branched-chain alkylthio groups having 1 to 6 carbon atoms such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, tert-butylthio, pentylthio, hexylthio.

[0016] As the lower alkanoyl group, there can be mentioned straight-chain or branched-chain alkanoyl groups having 1 to 6 carbon atoms such as formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, tert-butylcarbonyl, hexanoyl.

[0017] The lower alkoxycarbonyl group can be exemplified by straight-chain or branched-chain alkoxycarbonyl groups having 1 to 6 carbon atoms such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl.

[0018] As to the alkyl group, there can be mentioned, in addition to the lower alkyl groups metnioned above, straight-chain or branched-chain alkyl groups having 1 to 18 carbon atoms such as heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, octadecyl.

[0019] The C_1-C_6 alkyl group having hydroxyl groups can be exemplified by C_{1-6} straight-chain or branched-chain alkyl groups each having one to three hydroxyl groups, such as hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, 2,3-dihydroxypropyl, 4-hydroxybutyl, 1,1-dimethyl-2-hydroxyethy, 5,5,4-trihydroxypentyl, 5-hydroxypentyl, 6-hydroxyhexyl, 1-hydroxyisopropyl, 2-methyl-3-hydroxypropyl.

[0020] The phenyl group which may have one to three alkoxy groups as substituents on the phenyl ring, can be exemplified by phenyl rings which may each have one to three C_{1-6} straight-chain or branched-chain alkoxy groups as substituents on the phenyl ring, such as phenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 4-isopropoxyphenyl, 4-pentyloxyphenyl, 4-hexyloxyphenyl, 3,4-dimethoxyphenyl, 3-ethoxy-4-methoxyphenyl, 2,3-dimethoxyphenyl, 3,4-diethoxyphenyl, 2,5-dimethoxyphenyl, 2,6-dimethoxyphenyl, 3-propoxy-4-methoxyphenyl, 3,5-dimethoxyphenyl, 3,4-dipentyloxyphenyl, 3,4,5-trimethoxyphenyl, 3-methoxy-4-ethoxyphenyl.

[0021] The amino-C_1-C_6 alkoxycarbonyl group which may have a C_1-C_6 alkyl group as a substituent, can be exemplified by C_{1-6} straight-chain or branched-chain alkoxycarbonyl groups each having an amino group which may have one to two C_{1-6} straight-chain or branched-chain alkyl groups as substituents, such as aminomethoxycarbonyl, 2-aminoethoxycarbonyl, 1-aminoethoxycarbonyl, 3-aminopropoxycarbonyl, 4-aminobutoxycarbonyl, 5-aminopentyloxycarbonyl, 6-aminohexyloxycarbonyl, 1,1-dimethyl-2-aminoethoxycarbonyl, 2-methyl-3-aminopropoxycarbonyl, methylaminomethoxycarbonyl, 1-ethylaminoethoxycarbonyl, 2-propylaminoethoxycarbonyl, 3-isopropylaminopropoxycarbonyl, 4-butylaminobutoxycarbonyl, 5-pentylaminopentyloxycarbonyl, 6-hexylaminohexyloxycarbonyl, dimethylaminomethoxy-

carbonyl, 2-dimethylaminoethoxycarbonyl, 3-dimethylaminopropoxycarbonyl, (N-ethyl-N-propylamino)-methoxycarbonyl, 2-(N-methyl-N-hexylamino)ethoxycarbonyl.

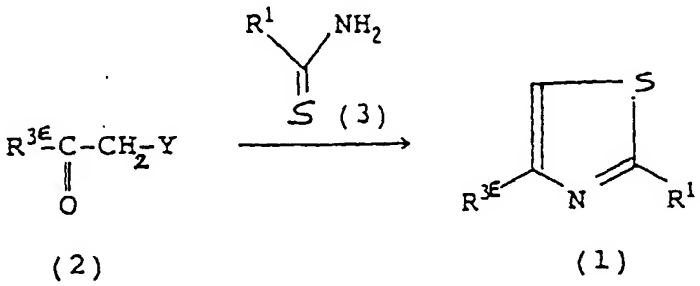
[0022] The five- or six-membered saturated heterocyclic ring which R^{23} and R^{24} as well as the adjacent nitrogen atom being bonded thereto may form together with or without other nitrogen atom or oxygen atom, can be exemplified by piperazinyl, pyrrolidinyl, morpholinyl and piperidinyl.

[0023] The above heterocyclic ring substituted with a C_1-C_6 alkyl group can be exemplified by above heterocyclic rings each substituted with a C_{1-6} straight-chain or branched-chain alkyl group, such as 4-methylpiperazinyl, 4-ethylpiperazinyl, 3-ethylpyrrolidinyl, 2-propylpyrrolidinyl, 4-butylpiperidinyl, 3-pentylmorpholino, 2-hexylpiperazinyl.

[0024] The thiazole derivatives according to the present invention can be produced by, for example, the processes shown below.

[Reaction scheme-1]

[0025]



(2) (1)

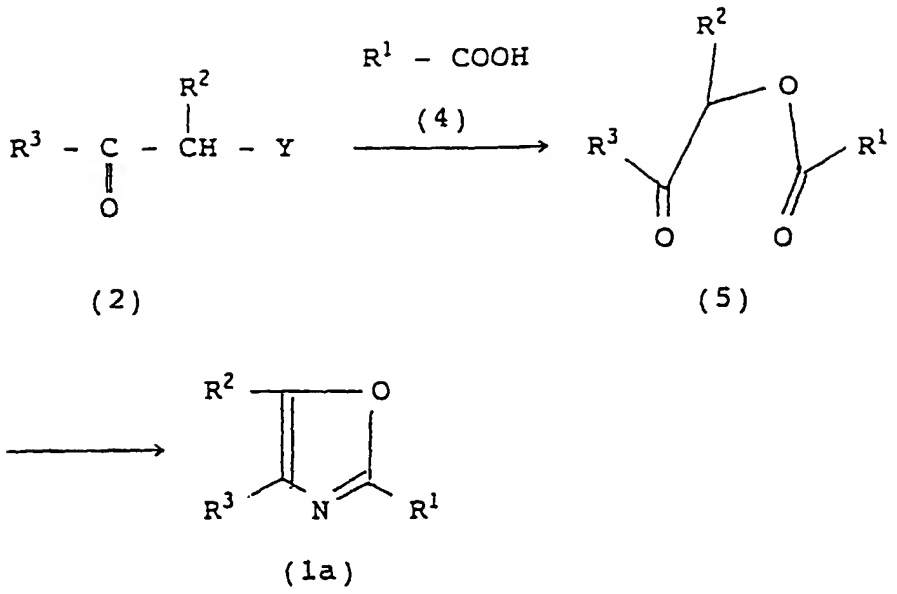
(wherein R^1 and R^{3E} are the same as defined above; Y represents a halogen atom).

[0026] The reaction between the compound (2) and the compound (3) can be conducted by heating in an appropriate solvent. The solvent can be exemplified by alcohols such as methanol, ethanol, propanol, butanol, 3-methoxy-1-butanol, ethyl cellosolve, methyl cellosolve; aromatic hydrocarbons such as benzene, toluene, xylene, o-dichlorobenzene; ethers such as diethyl ether, tetrahydrofuran, dioxane, diglyme, monoglyme; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride; polar solvents such as dimethylformamide, dimethyl sulfoxide, hexamethyl-phosphoric triamide, acetonitrile; and mixed solvents thereof. The reaction is conducted ordinarily at room temperature to 150°C, preferably at about room temperature to 100°C and is completed in about 1-15 hours.

[0027] The proper amount of the compound (3) used is at least 1 mole, preferably about 1 to 1.5 moles per 1 mole of the compound (2).

[Reaction scheme-2] (not in accordance with this invention)

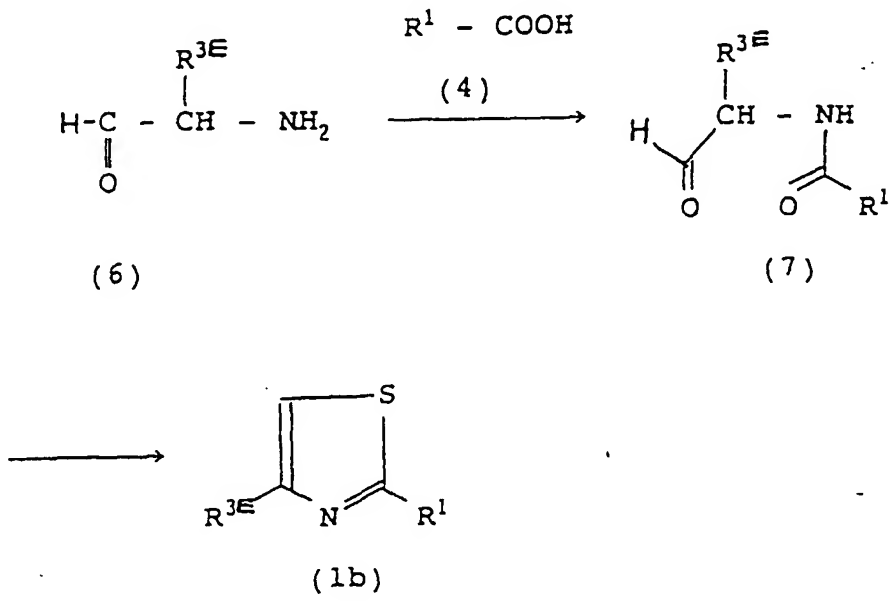
[0028]



[0029] The reaction between the compound (2) and the compound (4) can be conducted in an appropriate solvent in the presence of a basic compound. The solvent can be exemplified by lower alcohols such as methanol, ethanol, propanol; ethers such as diethyl ether, tetrahydrofuran, dioxane, ethylene glycol monomethyl ether; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride; aromatic hydrocarbons such as benzene, toluene, xylene; esters such as methyl acetate, ethyl acetate; ketones such as acetone, methyl ethyl ketone; polar solvents such as acetonitrile, dimethylformamide, dimethyl sulfoxide, hexamethylphosphoric triamide; and mixed solvents thereof. The basic compound can be exemplified by inorganic bases such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium hydride; alkali metals such as metallic sodium, metallic potassium; alkali metal alcoholates such as sodium methylate, sodium ethylate; and organic bases such as triethylamine, pyridine, N,N-dimethylaniline, N-methylmorpholine, 4-methylaminopyridine, bicyclo[4,3,0]nonene-5 (DBN), 1,8-diazabicyclo[5,4,0]-undecene-7 (DBU), 1-4-diazabicyclo[2,2,2]octane (DABCO).

[Reaction scheme-3]

[0030]



(wherein R^1 and R^{3E} are the same as defined above).

[0031] The reaction between the compound (6) and the compound (4) can be achieved by subjecting them to an ordinary amide bonding formation reaction.

[0032] In this case, as to the carboxylic acid (4), an activated compound thereof may be used. The conditions used in the amide bonding formation reaction can be those used in ordinary amide bonding formation reactions. For example, there can be used (a) a mixed acid anhydride method, i.e. a method which comprises reacting a carboxylic acid (4) with an alkylhalocarboxylic acid to obtain a mixed acid anhydride and reacting the anhydride with a compound (6); (b) an active ester or active amide method, i.e. a method which comprises converting a carboxylic acid (4) into an active ester such as p-nitrophenyl ester, N-hydroxysuccinimide ester, 1-hydroxybenzotriazole ester or the like, or into an active amide with benzoxazolin-2-thion and then reacting the active ester or active amide with a compound (6); (c) a carbodiimide method, i.e. a method which comprises subjecting a carboxylic acid (4) and a compound (6) to dehydration in the presence of a dehydrating agent such as dicyclohexylcarbodiimide, carbonyldiimidazole; (d) a carboxylic acid halide method, i.e. a method which comprises converting a carboxylic acid (4) into a halide and reacting the halide with a compound (6); and (e) other methods such as a method which comprises reacting a carboxylic acid (4) with a dehydrating agent such as acetic anhydride to convert into a carboxylic acid anhydride and reacting the anhydride with a compound (4) or a method which comprises converting a carboxylic acid (4) into an ester and reacting the ester with a compound (6) at a high temperature at a high pressure. There can also be used a method which comprises activating a carboxylic acid (4) with a phosphorus compound such as triphenylphosphine, diethyl chlorophosphate and reacting the reaction product with a compound (6).

[0033] As to the alkylhalocarboxylic acid used in the mixed acid anhydride method, there can be mentioned, for example, methyl chloroformate, methyl bromoformate, ethyl chloroformate, ethylbromoformate and isobutyl chloroformate. The mixed acid anhydride can be obtained by an ordinary Schotten-Baumann reaction and ordinarily, without being subjected to an isolation procedure, is reacted with a compound (6), whereby a compound (7) can be produced. The Schotten-Baumann reaction is ordinarily conducted in the presence of a basic compound. The basic compound is those conventionally used in the Schotten-Baumann reaction; and there can be mentioned organic bases such as triethylamine, trimethylamine, pyridine, dimethylaniline, N-methylmorpholine, 4-dimethylaminopyridine, DBN, DBU, DABCO, and inorganic bases such as potassium carbonate, sodium carbonate, potassium hydrogencarbonate, sodium hydrogencarbonate. The reaction is conducted at about -20°C to 100°C, preferably 0-50°C. The reaction time is about 5 minutes to 10 hours, preferably 5 minutes to 2 hours. The reaction between the thus obtained mixed acid anhydride and

the compound (6) is conducted at about -20°C to 150°C, preferably 10-50°C for about 5 minutes to 10 hours, preferably about 5 minutes to 5 hours. The mixed acid anhydride method needs no solvent, but is generally conducted in a solvent. The solvent can be any of those conventionally used in the mixed acid anhydride method, and there can be specifically mentioned, for example, halogenated hydrocarbons such as methylene chloride, chloroform, dichloroethane, aromatic hydrocarbons such as benzene, toluene, xylene and the like, ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran, dimethoxyethane, esters such as methyl acetate, ethyl acetate, and aprotic polar solvents such as dimethylformamide, dimethyl sulfoxide, hexamethylphosphoric triamide. In the above method, the amounts of the carboxylic acid (4), the alkylhalocarboxylic acid and the compound (6) used are ordinarily at least equimolar, but preferably the alkylhalocarboxylic acid and the compound (6) are used each in an amount of 1-2 moles per 1 mole of the carboxylic acid (4).

[0034] The active ester or active amide method (b), when a case of using, for example, benzoxazolin-2-thionamide is mentioned, is conducted by carrying out a reaction at 0-150°C, preferably 10-100°C for 0.5-75 hours in an appropriate solvent not affecting the reaction, for example, the same solvent as used in the above mixed acid anhydride method, or 1-methyl-2-pyrrolidone. The amounts of the compound (6) and benzoxazolin-2-thionamide used are such that the latter is used in an amount of at least 1 mole, preferably 1-2 moles per 1 mole of the former. In a case using an N-hydroxysuccinimide ester, the reaction proceeds advantageously by using an appropriate base, for example, the same base as used in the carboxylic acid halide method to be described later.

[0035] The carboxylic acid halide method (c) is conducted by reacting a carboxylic acid (4) with a halogenating agent to convert into a carboxylic acid halide and, after or without isolating and purifying the halide, reacting the halide with a compound (6). The reaction between the carboxylic acid halide and the compound (6) is conducted in an appropriate solvent in the presence or absence of a dehydrohalogenating agent. As to the dehydrohalogenating agent, there is ordinarily used a basic compound, and there can be mentioned the basic compounds used in the above Schotten-Baumann reaction, sodium hydroxide, potassium hydroxide, sodium hydride, potassium hydride, alkali metal alcholates (e.g. sodium methylate, sodium ethylate).

[0036] Incidentally, it is possible to use the compound (6) in an excessive amount to utilize the compound (6) also as a dehydrohalogenating agent. As the solvent, there can be mentioned, for example, water, alcohols (e.g. methanol, ethanol, propanol, butanol, 3-methoxy-1-butanol, ethyl cellosolve, methyl cellosolve), pyridine, acetone, acetonitrile and mixed solvents thereof, in addition to the same solvents as used in the above Schotten-Baumann reaction. The proportions of the compound (6) and the carboxylic acid halide used are not particularly restricted and can be selected from a wide range, but the latter is used in an amount of ordinarily at least 1 mole, preferably 1-5 moles per 1 mole of the former. The reaction is conducted ordinarily at about - 30°C to 180°C, preferably at about 0-150°C and is complete generally in 5 minutes to 30 hours. The carboxylic acid halide used is produced by reacting a carboxylic acid (4) with a halogenating agent in the presence or absence of a solvent. The solvent can be any as long as it gives no influence on the reaction, and includes aromatic hydrocarbons such as benzene, toluene, xylene and the like, halogenated hydrocarbons such as chloroform, methylene chloride, carbon tetrachloride, ethers such as dioxane, tetra-hydrofuran, diethyl ether, dimethylformamide, dimethyl sulfoxide. As the halogenating agent, there can be used ordinary halogenating agents capable of converting the hydroxyl group of carboxylic group into a halogen, and there can be mentioned, for example, thionyl chloride, oxalyl chloride, phosphorus oxychloride, phosphorus oxybromide, phosphorus pentachloride and phosphorus pentabromide. The proportions of the carboxylic acid (4) and the halogenating agent used are not particularly restricted and can be selected appropriately; however, when the reaction is conducted in a solventless state, the latter is used ordinarily in a large excess relative to the former and, when the reaction is conducted in a solvent, the latter is used in an amount of ordinarily at least about 1 mole, preferably 2-4 moles per 1 mole of the former. The reaction temperature and time are not particularly restricted, either, but the reaction is conducted ordinarily at about room temperature to 100°C, preferably at 50-80°C for about 30 minutes to 6 hours.

[0037] The method which comprises activating a carboxylic acid (4) with a phosphorus compound such as triphenylphosphine, diethyl chlorophosphate, diethyl cyanophosphate or the like and then reacting the resulting product with a compound (6), is conducted in an appropriate solvent. The solvent can be any as long as it gives no influence on the reaction, and specifically includes halogenated hydrocarbons such as dichloromethane, chloroform, dichloroethane, aromatic hydrocarbons such as benzene, toluene, xylene, ethers such as diethyl ether, tetrahydrofuran, dimethoxyethane, esters such as methyl acetate, ethyl acetate, aprotic polar solvents such as dimethylformamide, dimethyl sulfoxide, hexamethylphosphoric triamide. In the reaction, the compound (6) per se acts as a basic compound, and accordingly the reaction proceeds advantageously by using it in an amount larger than the stoichiometric amount; however, there may be used, as necessary, other basic compound, for example, an organic base (e.g. triethylamine, trimethylamine, pyridine, dimethylaminopyridine, DBN, DBU, DABCO) or an inorganic base (e.g. potassium carbonate, sodium carbonate, potassium hydrogencarbonate, sodium hydrogencarbonate). The reaction is conducted at about 0-150°C, preferably at about 0-100°C and is complete in about 1-30 hours. The proportions of the phosphorus compound and carboxylic acid (4) used relative to the compound (6) are each ordinarily at least about 1 mole, preferably 1-3 moles per 1 mole of the compound (6).

[0038] The reaction for converting the compound (7) into the compound (1b) can be conducted in a solventless state or in an appropriate solvent in the presence of a sulfurizing agent such as 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetan-2,4-disulfide (Lawesson's Reagent), phosphorus pentasulfide. The solvent can be any of those used in the reaction between the compound (2) and the compound (4) in the above Reaction scheme-2.

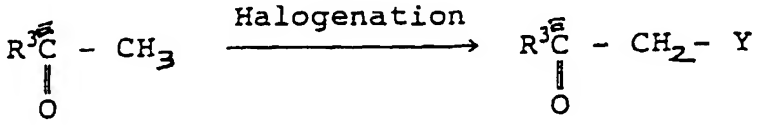
[0039] The proper amount of the sulfurizing agent used is ordinarily 0.5-2 moles, preferably 0.5-1.5 moles per 1 mole of the compound (7).

[0040] The reaction is conducted ordinarily at 50-300°C, preferably at about 50°C to 250°C and is completed in about 1-7 hours.

[0041] The compound (2) as a starting material can be produced by, for example, the method of the following Reaction scheme-4 or -5.

[Reaction scheme-4]

[0042]



(8) (2)

(wherein R^{3E} and Y are the same as defined above).

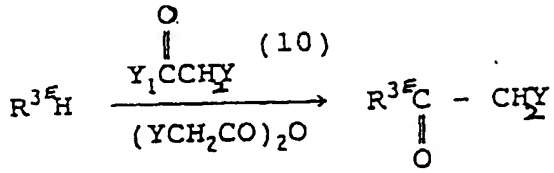
[0043] The halogenation reaction for the compound (8) can be conducted in an appropriate solvent in the presence of a halogenating agent. The halogenating agent can be exemplified by halogen molecules (e.g. bromine molecules, chlorine molecules), iodine chloride, sulfuryl chloride, copper compounds (e.g. cuprous bromide) and N-halogenated succinimides (e.g. N-bromosuccinimide, N-chlorosuccinimide). The solvent can be exemplified by halogenated hydrocarbons (e.g. dichloromethane, dichloroethane, chloroform, carbon tetrachloride), fatty acids (e.g. acetic acid, propionic acid) and carbon disulfide.

[0044] The proper amount of the halogenating agent used is ordinarily 1-10 moles, preferably 1-5 moles per 1 mole of the compound (8).

[0045] The reaction is conducted ordinarily at 0°C to the boiling point of the solvent used, preferably at about 0°C to 100°C and is completed ordinarily in about 5 minutes to 20 hours.

[Reaction scheme-5]

[0046]



(9) (11) (2a)

(wherein R^{3E} and Y are the same as defined above; and Y_1 represents a halogen atom)

[0047] The reaction between the compound (9) and the compound (10) or the compound (11) is generally called as Friedel-Crafts reaction and can be conducted in an appropriate solvent in the presence of a Lewis acid. The Lewis acid can be any one of Lewis acids generally used in said reaction, and can be exemplified by aluminum chloride, zinc chlo-

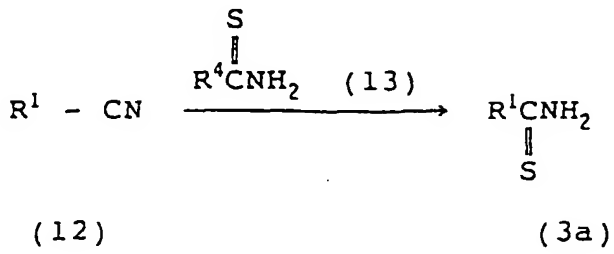
ride, iron chloride, tin chloride, boron tribromide, boron trifuloride and concentrated sulfuric acid. The solvent can be exemplified by carbon disulfide, aromatic hydrocarbons (e.g. nitrobenzene, chlorobenzene) and halogenated hydrocarbons (e.g. dichloromethane, dichloroethane, carbon tetrachloride, tetrachloroethane). The proper amount of the compound (10) or the compound (11) used is at least 1 mole, preferably 1-5 moles per 1 mole of the compound (9). The proper amount of the Lewis acid used is ordinarily 2-6 moles per 1 mole of the compound (9).

[0048] The reaction is conducted ordinarily at 0-120°C, preferably at about 0-70°C and is completed in about 0.5-24 hours.

[0049] The compound (3) as a starting material can be produced by, for example, the method of the following Reaction scheme-6 or -7.

[Reaction scheme-6]

[0050]



(R^1 is the same as defined above; R^4 represents a lower alkyl group).

[0051] The reaction between the compound (12) and the compound (13) can be conducted in an appropriate solvent in the presence of an acid.

[0052] The solvent can be any of those used in the reaction between the compound (2) and the compound (4) in the reaction scheme 2.

[0053] The acid can be exemplified by mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid.

[0054] The amount of the compound (13) used is ordinarily 1-5 moles, preferably 1-3 moles per 1 mole of the compound (12).

[0055] The reaction is conducted ordinarily at room temperature to 200°C, preferably at about room temperature to 150°C and is complete in about 1-15 hours.

[Reaction scheme-7]

[0056]

(wherein R^1 is the same as defined above).

[0057] The reaction for converting the compound (14) into the compound (3b) can be conducted in an appropriate solvent in the presence of a sulfurizing agent.

[0058] The solvent can be any of those used in the reaction between the compound (2) and the compound (4) in the reaction scheme 2.

[0059] The sulfurizing agent can be exemplified by phosphorus pentasulfide and Lawesson's Reagent.

[0060] The proper amount of the sulfurizing agent used is ordinarily 1-10 moles, preferably 1-2 moles per 1 mole of the compound (14).

[0061] The reaction is conducted ordinarily at room temperature to 150°C, preferably at about room temperature to 100°C and is complete in about 10 minutes to 5 hours.

[0062] When in general formula (1), R^1 or R^3 is a 5-to 15-membered monocyclic, bicyclic or tricyclic heterocyclic residual group having at least one oxo group adjacent to the nitrogen atom of the heterocyclic ring, the compound (1) can be converted, by reduction, into a corresponding compound where said at least one oxo group is converted into a methylene group.

[0063] The reduction can be conducted by, for example, catalytic hydrogenation in an appropriate solvent in the presence of a catalyst. As to the solvent, there can be mentioned, for example, water, acetic acid, alcohols (e.g. methanol, ethanol, isopropanol), hydrocarbons (e.g. hexane, cyclohexane), ethers (e.g. diethylene glycol dimethyl ether, dioxane, tetrahydrofuran, diethyl ether), esters (e.g. ethyl acetate, methyl acetate), aprotic polar solvents (e.g. dimethylformamide) and mixed solvents thereof. As to the catalyst, there can be used, for example, palladium, palladium black, palladium-carbon, platinum, platinum oxide, copper chromite and Raney nickel. The proper amount of the catalyst used is generally about 0.02-1 time the weight of the starting material. Desirably, the reaction temperature is ordinarily about -20°C to 100°C, preferably about 0-70°C and the hydrogen pressure is ordinarily 1-10 atm. The reaction is complete generally in about 0.5-20 hours. The reduction may be conducted by catalytic hydrogenation, but can be conducted preferably by a method using a hydride reducing agent. As the hydride reducing agent, there can be mentioned, for example, lithium aluminum hydride, sodium boron hydride and diborane. The amount of the hydride reducing agent used is ordinarily at least 1 mole, preferably 1-15 moles per 1 mole of the starting compound. The reduction reaction is conducted ordinarily at about -60°C to 150°C, preferably at -30°C to 100°C for about 10 minutes to 10 hours, ordinarily using an appropriate solvent, for example, water, a lower alcohol (e.g. methanol, ethanol, isopropanol), an ether (e.g. tetrahydrofuran, diethyl ether, diisopropyl ether, diglyme) or a mixture thereof. The use of an anhydrous solvent such as diethyl ether, diisopropyl ether, tetrahydrofuran, diglyme is preferred when the reducing agent used is lithium aluminum hydride or diborane.

[0064] When in the compound (1), R^{3E} is a pyridyl group or a furyl group having at least one lower alkoxycarbonyl group, the R^{3E} can be converted, by hydrolysis, into a corresponding group having at least one carboxy group.

[0065] The hydrolysis reaction can be conducted under any conditions ordinarily employed in hydrolysis. It is specifically conducted in the presence of a basic compound (e.g. sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide or barium hydroxide), a mineral acid (e.g. sulfuric acid, hydrochloric acid or nitric acid), an organic acid (e.g. acetic acid or aromatic sulfonic acid) in a solvent such as water, alcohol (e.g. methanol, ethanol or isopropanol), ketone (e.g. acetone or methyl ethyl ketone), ether (e.g. dioxane or ethylene glycol dimethyl ether), acetic acid, or in a mixed solvent thereof. The reaction proceeds ordinarily at room temperature to 200°C, preferably at about from room temperature to 180°C and is completed generally in about 10 minutes to 30 hours.

[0066] When in the compound (1), R^{3E} is a pyridyl group or furyl group having at least one carboxy group, R^{3E} can be converted, by an esterification reaction, into a corresponding group having at least one lower alkoxycarbonyl group.

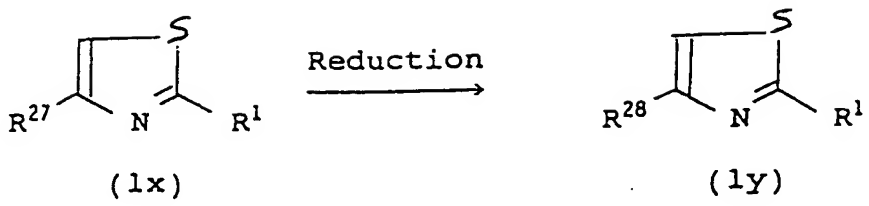
[0067] The esterification reaction can be conducted by reacting the compound (1) with an alcohol such as methyl alcohol, ethyl alcohol, isopropyl alcohol, benzyl alcohol, in the presence of a mineral acid (e.g. hydrochloric acid, sulfuric acid) and a halogenating agent (e.g. thionyl chloride, phosphorus oxychloride, phosphorus pentachloride, phosphorus trichloride) ordinarily at 0-150°C, preferably at 50-100°C for about 1-10 hours.

[0068] When in the compound (1), R^{3E} is a pyridyl group or a furyl group having at least one nitrile group or at least one carbamoyl group as substituent(s), then R^{3E} can be converted, by hydrolysis, into a corresponding group having at least one carboxy group as substituent(s).

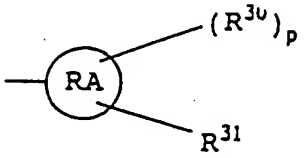
[0069] The hydrolysis reaction can be conducted under the same conditions as employed in the hydrolysis reaction for the compound (1) where R^{3E} is a pyridyl group or a furyl group having at least one alkoxycarbonyl group.

[Reaction scheme-20]

[0070]

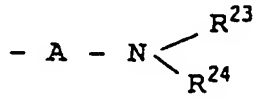


{wherein R^1 is the same as defined above. R^{27} represents a group of the formula,

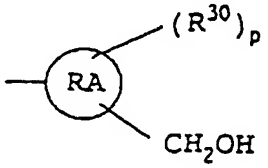


[the group of

represents a pyridyl group or a furyl group, R^{30} represents an alkyl group, a benzoyl group, a C_{1-6} alkanoyl group, a hydroxyl group, a carboxy group, a C_{1-6} alkoxycarbonyl group, a C_{1-6} alkylthio group, a group of the formula,



(A is the same as above. R^{23} and R^{24}, which may be the same or different, each represent a hydrogen atom or a C_{1-6} alkyl group; R^{23} and R^{24} as well as the nitrogen atom being bonded thereto, together with or without other nitrogen atom or oxygen atom, may form a 5- to 6-membered saturated heterocyclic ring. The heterocyclic ring may have a C_{1-6} alkyl group as a substituent.); a cyano group, a C_{1-6} alkyl group having hydroxyl groups, a phenylaminothiocarbonyl group and an amino-C_{1-6} alkoxycarbonyl group which may have a C_{1-6} alkyl group as a substituent. R^{31} represents a formyl group or a lower alkoxycarbonyl group. p represents 0 or an integer of 1 or 2 provided that when the group (RA) is a furyl group, then p represents an integer of 1 or 2.] R^{28} represents a group of the formula,



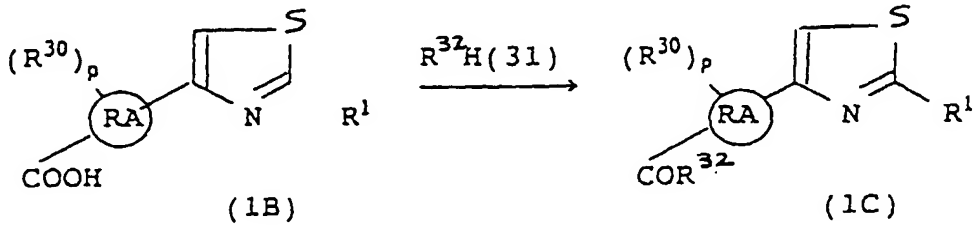
(the group of

R^{30} and p are the same as defined above).}

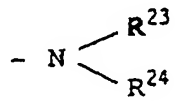
[0071] The reduction of the compound (1x) can be conducted under the same conditions as employed in the reduction conducted using a hydride reducing agent for the compound (1) where R^1 or R^{3E} is a 5- to 15-membered monocyclic, bicyclic or tricyclic heterocyclic residual group having at least one oxo group adjacent to the nitrogen atom of the heterocyclic ring.

[Reaction scheme-21]

[0072]



[wherein R^1 R^{30}, p and (RA) are the same as defined above; R^{32} represents a group of the formula,

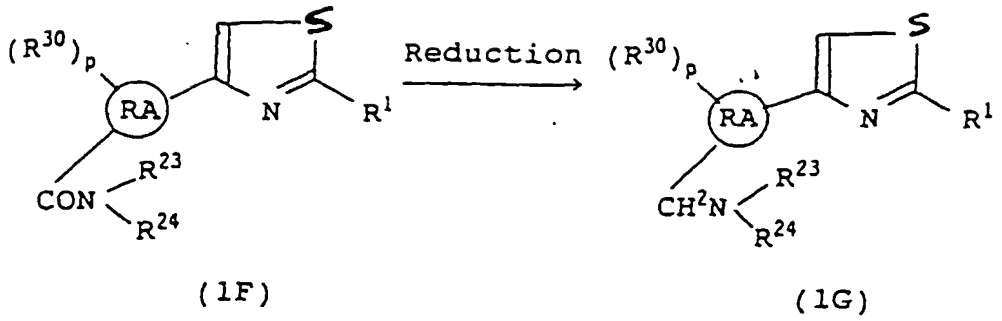


(R^{23} and R^{24} are the same as defined above) or an amino-lower alkoxy group which may have a lower alkyl group as a substituent.]

[0073] The reaction between the compound (1B) and the compound (31) can be conducted under the same conditions as employed in the reaction between the compound (6) and the compound (4) in the Reaction scheme 3.

[Reaction scheme-22]

[0074]

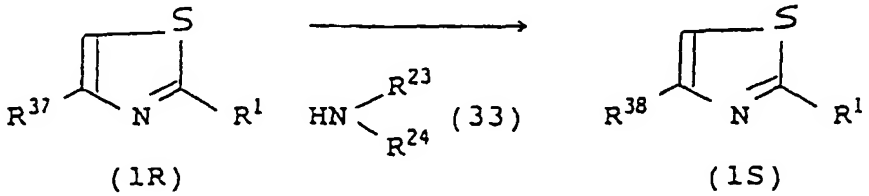


(wherein R^1, R^{30}, p, R^{23}, R^{24} and (RA) are the same as defined above.)

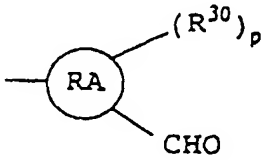
[0075] The reduction of the compound (1F) can be conducted under the same conditions as employed in the reduction reaction for the compound (1) where R^1 or R^{3E} is a 5- to 15-membered monocyclic, bicyclic or tricyclic heterocyclic residual group having at least one oxo group adjacent to the nitrogen atom of the heterocyclic ring.

[Reaction scheme-25]

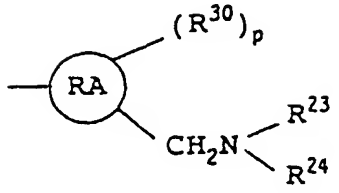
[0076]



[wherein R^1 is the same as defined above; R^{37} represents a group of the formula,



(RA, R^{30} and p are the same as defined above); R^{38} represents a group of the formula,

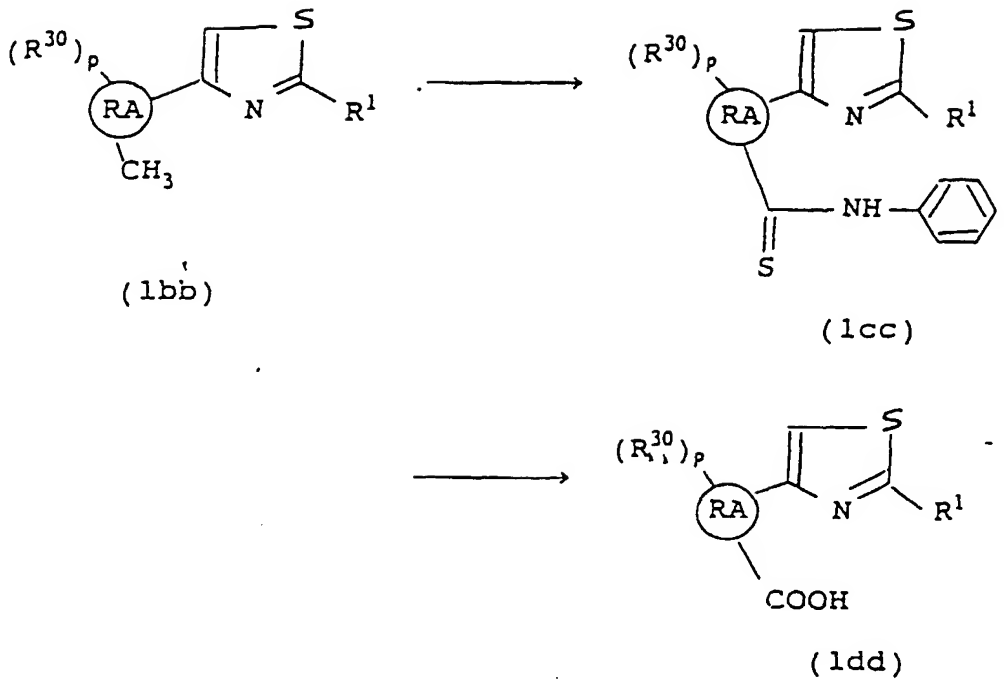


(R^{30}, R^{23}, R^{24}, RA and p are the same as defined above)].

[0077] The reaction between the compound (1R) and the compound (33) is conducted in the absence of a solvent or in an appropriate solvent in the presence of a reducing agent. The solvent can be exemplified by water; alcohols such as methanol, ethanol, isopropanol; acetic acid; ethers such as dioxane, tetrahydrofuran, diethyl ether, diglyme; and aromatic hydrocarbons such as benzene, toluene, xylene. The reduction method can be exemplified by a method using formic acid or a hydride reducing agent such as sodium boron hydride, sodium cyanoborohydride, lithium aluminum hydride, and a catalytic reduction method using a catalytic reduction catalyst such as palladium black, palladium-carbon, platinum oxide, platinum black, Raney nickel. When formic acid is used as the reducing agent, the appropriate reaction temperature is ordinarily room temperature to 200°C, preferably about 50-150°C, and the reaction is complete in about 1-10 hours. The proper amount of formic acid used is a large excess relative to the compound (1R). When a hydride reducing agent is used, the appropriate reaction temperature is ordinarily -30°C to 100°C, preferably about 0-70°C, and the reaction is complete in about 30 minutes to 20 hours. The proper amount of the reducing agent is ordinarily 1-20 moles, preferably 1-15 moles per 1 mole of the compound (1R). In particular, when lithium aluminum hydride is used as the reducing agent, it is preferable to use, as a solvent, an ether such as dioxane, tetrahydrofuran, diethyl ether, diglyme, or an aromatic hydrocarbon such as benzene, toluene, xylene. When a catalytic reduction catalyst is used, the reaction is conducted in a hydrogen atmosphere of ordinarily normal pressure to 20 atm., preferably normal pressure to 10 atm. ordinarily at -30°C to 100°C, preferably at 0-60°C. The proper amount of the catalyst used is ordinarily 0.1-40% by weight, preferably 1-20% by weight based on the compound (1R). The proper amount of the compound (33) used is ordinarily 1 mole per 1 mole of the compound (1R), preferably equimolar to a large excess relative to the compound (1R).

[Reaction scheme-27]

[0078]



(wherein R^1, (RA), R^{30} and p are the same as above.)

[0079] The reaction for converting the compound (1bb) into a compound (1cc) can be conducted by heating with aniline and sulfur in the absence of a solvent state.

[0080] The reaction is conducted ordinarily at 100-250°C, preferably at about 100-200°C, and is complete in about 1-20 hours.

[0081] The amounts of aniline and sulfur used are each ordinarily 1-10 moles, preferably 1-2 moles per 1 mole of the compound (1bb).

[0082] The reaction for converting the compound (1cc) into a compound (1dd) can be conducted under the same conditions as employed in the above-mentioned hydrolysis reaction for the compound (1) where R^{3E} is a pyridyl group or a furyl group having at least one alkoxycarbonyl group.

[0083] The products thus obtained in each step can be separated and purified by ordinary means. The separation means can be exemplified by solvent extraction, dilution, recrystallization, column chromatography and preparative thin-layer chromatography.

[0084] Needless to say, the compounds of the present invention include stereoisomers and optical isomers.

[0085] Of the thiazole derivatives represented by general formula (1) of the present invention, those compounds having acidic groups can be easily converted into respective salts by allowing a pharmceutically acceptable basic compound to act on the compounds. As the basic compound, there can be mentioned, for example, sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate and potassium hydrogencarbonate.

[0086] The compounds of the present invention are generally used in the form of ordinary pharmaceutical preparations. The pharmaceutical preparations are prepared using diluents or excipients ordinarily used, such as filler, bulking agent, binder, humectant, disintegrator, surfactant, lubricant. The pharmaceutical preparations can be used in various forms depending upon the purpose of remedy, and typical forms include tablets, pills, powders, solutions, suspensions, emulsions, granules, capsules, suppositories, injections (solutions, suspensions, etc.), ointments. In preparing tablets, various carriers conventionally known in the art can be used. The carriers can be exemplified by excipients such as lactose, white sugar, sodium chloride, grape sugar, urea, starch, calcium carbonate, kaolin, crystalline cellulose, silicic acid; binders such as water, ethanol, propanol, simple syrup, grape sugar solution, starch solution, gelation solution,

carboxymethyl cellulose, shellac, methyl cellulose, potassium phosphate, polyvinylpyrrolidone; disintegrators such as dry starch, sodium alginate, powdered agar, powdered laminaran, sodium hydrogencarbonate, calcium carbonate, polyoxyethylene sorbitan-fatty acid esters, sodium lauryl sulfate, stearic acid monoglyceride, starch, lactose and the like; disintegration inhibitors such as white sugar, stearin, cacao butter, hydrogenated oil; absorption promoters such as quaternary ammonium salts, sodium lauryl sulfate; humectants such as glycerine, starch; adsorbents such as starch, lactose, kaolin, bentonite, colloidal silicic acid; and lubricants such as refined talc, stearic acid salts, boric acid powder, polyethylene glycol. The tablets can be prepared, as necessary, in the form of ordinary coated tablets, such as sugar-coated tablets, enteric coated tablets or film-coated tablets, or in the form of double-layered tablets or multi-layered tablets. In preparing pills, various carriers conventionally known in the art can be used. The carriers can be exemplified by excipients such as grape sugar, lactose, starch, cacao butter, hardened vegetable oils, kaolin, talc; binders such as powdered acacia, powdered tragacanth, gelatin, ethanol; and disintegrators such as laminaran, agar. In preparing suppositories, various carriers conventionally known in the art can be used. The carriers can be exemplified by a polyethylene glycol, cacao butter, a higher alcohol, a higher alcohol ester, gelatin and a semi-synthetic glyceride. In preparing injections (solutions, emulsions, suspensions), they are sterilized and preferably isotonic to blood. In preparing these solutions, emulsions and suspensions, there can be used all of the diluents conventionally used in the art, such as water, aqueous lactic acid solution, ethyl alcohol, propylene glycol, ethoxylated isostearyl alcohol, polyoxyisostearyl alcohol and polyoxyethylene sorbitan-fatty acid ester. In this case, the injections may contain sodium chloride, grape sugar or glycerine in an amount sufficient to make the injections isotonic, and may further contain a solubilizing agent, a buffer solution, a soothing agent, all ordinarily used. The pharmaceutical preparations may furthermore contain, as necessary, a coloring agent, a preservative, a perfume, a flavoring agent, a sweetening agent and other drugs. In preparing pastes, creams and gels, there can be used various diluents conventionally known in the art, such as white petrolatum, paraffin, glycerine, cellulose derivative, polyethylene glycol, silicon, bentonite.

[0087] The amount of the present compound of general formula (1) or a salt thereof to be contained in a pharmaceutical preparation is not particularly restricted and can be appropriately selected in a wide range, but preferably is ordinarily 1-70% by weight in the pharmaceutical preparation.

[0088] The method for administering the pharmaceutical preparation is not particularly restricted. The pharmaceutical preparation can be administered in various methods depending upon the form of preparation, the age, sex and other conditions of patient, the degree of disease condition of patient. For example, tablets, pills, a solution, a suspension, an emulsion, granules or capsules are administered orally. An injection is intravenously administered singly or in admixture with an ordinary auxiliary solution of grape sugar, amino acid or the like, or, as necessary, is singly administered intramuscularly, intradermally, subcutaneously or intraperitoneally. Suppositories are administered intrarectally.

[0089] The dose of the pharmaceutical preparation of the present invention is appropriately selected depending upon the administration method, the age, sex and other conditions of patient, the degree of disease condition of patient, but preferably is ordinarily about 0.2-200 mg per kg of body weight per day in terms of the amount of the active ingredient.

Examples

[0090] The present invention is hereinafter described with reference to Reference Examples, Examples, Preparation Examples and Pharmacological Tests.

Reference Example 1

[0091] 25 g of 3,4-dimethoxybenzonitrile and 23 g of thioacetamide were dissolved in 120 ml of 10% hydrochloric acid-DMF. The solution was heated at 90°C for 3 hours. The solution was further heated at 130°C for 5 hours to conduct a reaction. The solvent was removed by distillation. The residue was washed twice with 100 ml of diethyl ether. Similar washing was conducted with 100 ml of water. The resulting crystals were collected by filtration and dried. Recrystallization from methanol was conducted to obtain 18.7 g of 3,4-dimethoxythiobenzamide as light brown columnar crystals.

M.p.: 170-175°C (decomposed)

NMR (CDC"3) δ:
3.94 (3H, s)
3.95 (3H, s)
6.83 (1H, d, J=8.4Hz),
7.15 (1H, brs),
7.38 (1H, dd, J-2.2Hz, 8.4Hz),
7.52 (1H, brs),
7.63 (1H, d, J=2.2Hz).

Reference Example 2

[0092] 500 mg of 3,4,5-trimethoxybenzamide was suspended in 15 ml of benzene. Thereto was added 526 mg of phosphorus pentasulfide. The mixture was refluxed for 30 minutes with heating. The solvent was removed by distillation. To the residue were added 5 ml of 10% sodium hydroxide and 5 ml of water. The mixture was stirred for 30 minutes. The reaction mixture was filtered, and the resulting solid was washed with small amounts of water and ethanol and dried to obtain 330 mg of 3,4,5-trimethoxythiobenzamide as a yellow powder.

M.p.: 182.5-184°C

Reference Example 3

[0093] 4 g of 3',5'-diacetyloxyacetophenone was suspended in 75 ml of carbon disulfide. Thereto was dropwise added a solution of 0.90 ml of bromine dissolved in 25 ml of carbon disulfide, at room temperature in about 1 hour. The system was heated to about 50°C ocassionally in the course of dropwise addition and, each time when a reaction started, the system was returned to room temperature and stirred. After the completion of the dropwise addition, stirring was conducted at room temperature for 1 hour. After the completion of the reaction, the solvent was removed by distillation to obtain 5.53 g of 3',5'-diacetyloxy-2-bromoacetophenone as brown crystals.

M.p.: 61-62°C

Reference Example 4

[0094] 5.47 g of chloroacetyl chloride was dissolved in 20 ml of dichloromethane. Thereto was added 6.46.g of finely ground aluminum chloride with ice-cooling. Stirring was conducted for 30 minutes. Thereto was added 2 g of 3,4-dihydro-2H-1,4-benzothiazin-3(4H)-one. The mixture was stirred for 4 hours with ice-cooling and then overnight at room temperature. The reaction mixture was poured into ice water. The resulting crystals were collected by filtration, water-washed and dried to obtain 3.03 g of 6-α-chloroacetyl-3,4-dihydro-2H-1,4-benzothiazin-3-one.

NMR (DNSO-d6) δ:
3.55 (2H, s),
5.10 (2H, s),
7.65-7.45 (3H, m),
10.76 (1H, s).

Reference Examples 11-13, 25 and 29

[0095] Compounds shown in Table 1 were obtained by using respective starting materials, in the same procedure as in Reference Example 1 or 2.

Table 1

$R^1C(=S)NH_2$

Reference Example	R^1	Properties
11		Crystal form: Yellow columnar (recrystallized from ethyl acetate-n-hexane) Mp: 116-117°C
12		Crystal form: Yellow columnar (recrystallized from ethyl acetate) Mp: 130-131°C
13		NMR (DMSO-d_6) δ: 3.80 (3H, s), 3.84 (3H, s), 6.50-6.63 (2H, m), 8.00-8.10 (1H, m), 9.14 (1H, brs), 9.79 (1H, brs)

Table 1 (Cont.)

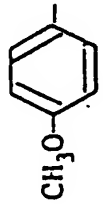
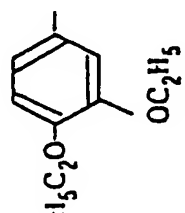
Reference Example	R^1	Properties
25		NMR ($CDCl_3$) δ: 8.0-7.85 (2H, m), 7.55 (1H, brs), 7.1 (1H, brs), 7.0-6.85 (2H, m), 3.86 (3H, s)

Table 1 (Cont.)

Reference Example	R^1	Properties
29		NMR (DMSO-d_6) δ: 9.62 (1H, brs), 9.30 (1H, brs), 7.65-7.5 (2H, m), 6.95 (1H, d, J=9.1Hz), 4.07 (2H, q, J=7Hz), 4.04 (2H, q, J=7Hz), 1.33 (6H, t, J=7Hz)

Reference Examples 62-69

[0096] Compounds shown in Table 3 where obtained by using respective starting materials, in the same procedure in Reference Example 1 or 2.

Table 3

R^1-C(=S)-NH_2

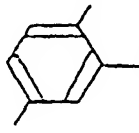
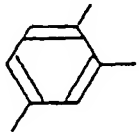
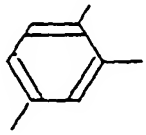
Reference Example	R^1	Properties
62		NMR (DMSO-d_6) δ: 0.86 (6H, brs), 1.10-1.53 (28H, m), 1.60-1.8 (4H, m), 3.85-4.15 (4H, m), 6.94 (1H, d, J=9.2Hz), 7.53-7.65 (2H, m), 9.29 (1H, brs), 9.61 (1H, brs)
63		NMR (DMSO-d_6) δ: 0.92 (6H, t, J=7.2Hz), 1.30-1.55 (4H, m), 1.55-1.81 (4H, m), 3.99 (4H, q, J=6.2Hz), 6.96 (1H, d, J=9.1Hz), 7.50-7.65 (1H, m), 9.30 (1H, brs), 9.62 (1H, brs)
64		NMR (DMSO-d_6) δ: 0.97 (6H, t, J=7.4Hz), 1.58-1.85 (4H, m) 3.95 (4H, q, J=6.4Hz), 6.96 (1H, d, J=9.1Hz), 7.50-7.62 (2H, m), 9.30 (1H, brs), 9.62 (1H, brs)

Table 3 (Cont.)

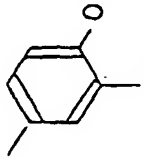
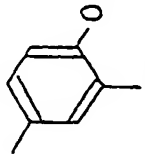
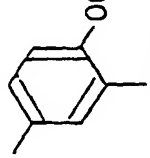
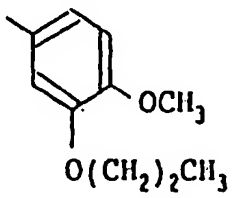
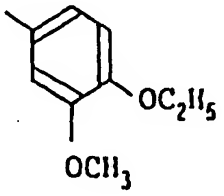
Reference Example	R^1	Properties
65		NMR (DMSO-d_6) δ: 0.96 (3H, t, J=7.3Hz), 1.61-1.86 (2H, m), 3.97 (3H, s), 3.96 (2H, t, J=6.6Hz), 6.96 (1H, d, J=9.2Hz), 7.50-7.62 (2H, m), 9.32 (1H, brs), 9.63 (1H, brs)
66		NMR (DMSO-d_6) δ: 0.92 (3H, t, J=7.2Hz), 1.30-1.55 (2H, m), 1.55-1.80 (2H, m), 3.78 (3H, s), 4.00 (2H, t, J=6.5Hz), 6.96 (1H, d, J=9.1Hz), 7.52-7.66 (2H, m), 9.31 (1H, brs), 9.63 (1H, brs)
67		NMR (DMSO-d_6) δ: 1.33 (3H, t, J=6.9Hz), 3.80 (3H, s), 4.04 (2H, q, J=6.9Hz), 6.96 (1H, d, J=8.2Hz), 7.50-7.66 (2H, m), 9.31 (1H, brs), 9.63 (1H, brs)

Table 3 (Cont.)

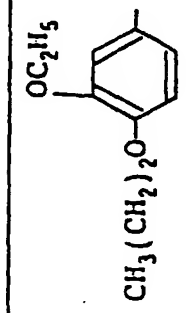
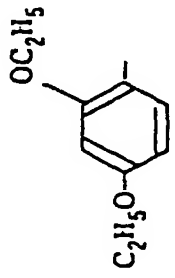
Reference Example	R^1	Properties
68		NMR (DMSO-d_6) δ: 0.97 (3H, t, J=7.4Hz), 1.63-1.88 (2H, m), 3.80 (3H, s), 3.94 (2H, t, J=6.6Hz), 6.96 (1H, d, J=8.3Hz), 7.53-7.67 (2H, m), 9.31 (1H, brs), 9.63 (1H, brs)
69		NMR (DMSO-d_6) δ: 1.33 (3H, t, J=7.0Hz), 3.78 (3H, s), 4.05 (2H, q, J=7.0Hz), 6.95 (1H, d, J=9.1Hz), 7.51-7.66 (2H, m), 9.31 (1H, brs), 9.64 (1H, brs)

Reference Examples 76-77

[0097] Compounds shown in Table 5 were obtained by using respective starting materials, in the same procedure as in Reference Examples 1 or 2.

Table 5

$R^1-C(=S)-CH_2$

Reference Example	R^1	Properties
76		NMR ($CDCl_3$) δ: 1.05 (3H, t, J=7.5Hz), 1.46 (3H, t, J=7.0Hz), 1.79-1.93 (2H, m), 4.02 (2H, t, J=6.8Hz), 4.13 (2H, q, J=7.0Hz), 6.85 (1H, d, J=8.4Hz), 7.16 (1H, brs), 7.37 (1H, dd, J=2.3Hz, 8.4Hz), 7.54 (1H, brs), 7.60 (1H, d, J=2.3Hz)
77		NMR ($CDCl^3$) δ: 1.43 (3H, t, J=7.0Hz), 1.50 (3H, t, J=7.0Hz), 4.01-4.23 (4H, m), 6.43 (1H, d, J=2.3Hz), 6.53 (1H, dd, J=9.0Hz, 2.3Hz), 7.98 (1H, brs), 8.69 (1H, d, J=9.0Hz), 9.23 (1H, brs)

Reference Examples 105, 106 and 108-115

[0098] Compounds shown in Table 7 were obtained using respective starting materials in the same procedure as in Reference Example 3 or 4.

Table 7

$$R^{3E}-\overset{O}{\overset{\|}{C}}-CH_2Y$$

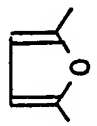
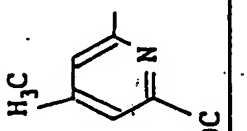
Reference Example	R^{3E}	Y	Crystal form (recrystallization solvent)	Melting point (°C) (salt form)
105		"		NMR[20] (-)
106		"		NMR[21] (-)

Table 7 (Cont.)

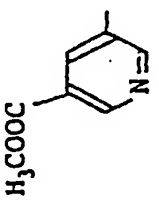
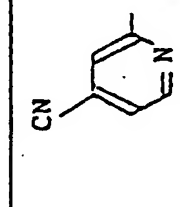
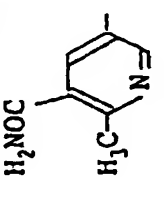
Reference Example		R^{3E}	Y	Crystal form (recrystallization solvent)	Melting point (°C) (salt form)
108			"		NMR[23] (HBr)
109			"		NMR[24] (HBr)
110			"		NMR[25] (HBr)

Table 7. (Cont.)

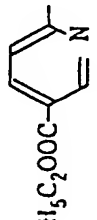
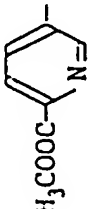
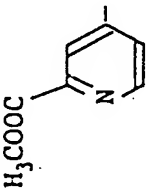
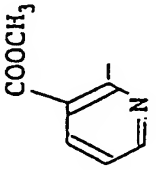
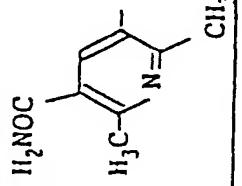
Reference Example		R^{3E}	Y	Crystal form (recrystallization solvent)	Melting point (°C) (salt form)
111			Br		NMR[26] (-)
112			"		NMR[27] (HBr)
113			"		NMR[28] (-)
114			"		NMR[29] (HBr)

Table 7 (Cont.)

Reference Example	R^{3E}	Y	Crystal form (recrystallization solvent)	Melting point (°C) (salt form)	$NMR^{30)}$ (HBr)
115		Br			

NMR data of the compounds of Reference Examples 105, 106, 108-115.

$NMR^{20)}$: Compound of Reference Example 105

^{1}H-NMR($CDCl_3$) δ: 3.95 (3H, s), 4.42 (2H, s),
7.26 (1H, d, J=3.7Hz),
7.34 (1H, d, J=3.7Hz)

NMR[21]: Compound of Reference Example 106

^{1}H-NMR($CDCl_3$) δ: 1.47 (3H, t, J=7.1Hz),
2.61 (3H, s), 4.46 (2H, q, J-7.1Hz), 5.00 (2H, s),
8.21 (2H, m)

NMR[23]: Compound of Reference Example 108

^{1}H-NMR($CDCl_3$) δ: 4.10 (3H, s), 4.92 (2H, s),
9.41-10.01 (3H, m)

NMR[24]: Compound of Reference Example 109

^{1}H-NMR(DMSO-d_6) δ:5.05 (2H, s), 8.20 (1H, dd, J=1.6Hz, 5.0Hz),
8.42 (1H, dd, J=0.9Hz, 1.6Hz),
9.01 (1H, dd, J=0.9Hz, 5.0Hz)

NMR[25]: Compound of Reference Example 110

^{1}H-NMR(DMSO-d_6) δ:2.73 (3H, s), 5.03 (2H, s),
8.17 (1H, brs), 8.26 (1H, brs),
8.44 (1H, d, J=2.1Hz),
8.54 (1H, d, J=2.1Hz)

NMR[26]: Compound of Reference Example 111

^{1}H-NMR($CDCl_3$) δ: 4.01 (3H, s), 4.88 (2H, s),
8.15 (1H, dd, J=0.7Hz, 8.1Hz),
8.45 (1H, dd, J=2.1Hz, 8.1Hz),
9.13 (1H, m)

NMR[27]: Compound of Reference Example 112

^{1}H-NMR($CDCl_3$) δ: 1.45 (3H, t, J=7.1Hz),
4.52 (2H, q, J=7.1Hz),
4.78 (2H, s),
8.49 (1H, d, J=8.1Hz)
8.96 (1H, dd, J=1.9Hz, 8.1Hz),
9.55 (1H, d, J=1.9Hz)

NMR[28]: Compound of Reference Example 113

^{1}H-NMR(DMSO-d_6) δ:2.77 (3H, s), 5.08 (2H, s),
8.11 (1H, d, J=5.7Hz),
8.25 (1H, s),
8.96 (1H, d, J=5.7Hz)

NMR[29]: Compound of Reference Example 114

^{1}H-NMR($CDCl_3$) δ: 4.11 (3H, s), 4.76 (2H, s),
7.60 (1H, dd, J=4.8Hz, 7.9Hz),
8.12 (1H, dd, J=1.5Hz, 7.9Hz),
8.96 (1H, dd, J=1.5Hz, 4.8Hz)

NMR[30]: compound of Reference Example 115

^{1}H-NMR(DMSO-d_6) δ:2.82 (3H, s), 2.87 (3H, s),
5.20 (2H, s), 8.09 (1H, brs),
8.42 (1H, brs), 9.01 (1H, s)

Example 1 (not in accordance with this invention)

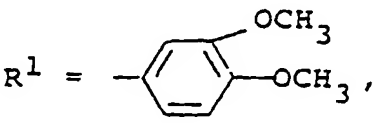
[0099] In 20 ml of ethanol were suspended 367 mg of 3',4'-dihydroxy-2-chloroacetophenone and 430 mg of 3,4-dimethoxythiobenzamide. The suspension was refluxed for 3 hours with heating. After cooling, the resulting crystals were collected by filtration, ethanol-washed and dried. The dried material was recrystallized from ethanol to obtain 160 mg of 2-(3,4-dimethoxyphenyl)-4-(3,4-dihydroxyphenyl)thiazole hydrochloride as yellow acicular crystals.

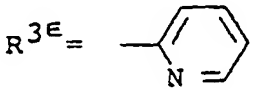
M.p.: 146-148°C

Example 133

[0100] The compound of Example 133 was obtained by using respective starting materials, in the same procedure as in Example 1.

Compound of Example 133





Crystal form: light yellow powdery (recrystallized from ethanol)

Mp: 157-167°C (decomposed, HCl salt)

NMR ($CDCl_3$) δ:

3.80(3H, s), 3.87(3H, s), 7.06(1H, d, J=8.5Hz),

7.56(1H, dd, J=2.1Hz, 8.5Hz), 7.65-7.82(2H, m),

8.31(1H, t, J=6.7Hz), 8.46(1H, d, J=7.9Hz),

8.65-8.82(2H, m)

Example 138 (not in accordance with this invention)

[0101] There were mixed, each in a powdery state, 500 mg of 6-[2-(3,4-dimethoxybenzoylamino)acetyl]-3,4-dihydrocarbostyril and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent). The mix-

ture was stirred at 200°C with heating. After 3 hours, the reaction was completed. The residue was subjected to silica gel column chromatography (dichloromethane:methanol = 49:1 by v/v). A solid obtained from the eluate was recrystallized from ethanol to obtain 98 mg of 2-(3,4-dimethoxyphenyl)-5-(3,4-dihydrocarbostyril-6-yl)thiazole as a white powder.

M.p. 235-236°C

[0102] The compound of Example 133 was obtained by using respective starting materials, in the same procedure as in Example 138.

Example 147 (not in accordance with the invention)

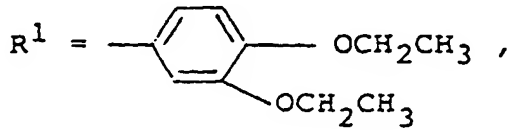
[0103] 2.05 g of 2-(4-ethoxycarbonylphenyl)-4-(3,4-dihydrocarbostyril-6-yl)thiazole was suspended in 20 ml of a 10% aqueous potassium hydroxide solution and 50 ml of ethanol. The suspension was refluxed for 5 hours. Ethanol was removed by distillation. After cooling, the residue was mixed with hydrochloric acid to make it acidic (pH 1). The resulting crystals were collected by filtration and recrystallized from dimethylformamide to obtain 0.70 g of 2-(4-carboxyphenyl)-4-(3,4-dihydrocarbostyril-6-yl)thiazole as a light yellow powder.

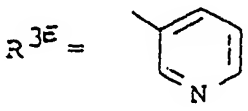
M.p.: 300°C or above

Examples 221 and 225

[0104] Compounds of Examples 221 and 225 were obtained by using respective starting materials, in the same procedures as in Examples 1 and 138.

Compound of Example 221

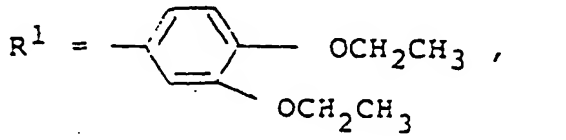


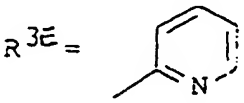


Crystal form: white acicular (recrystallized from ethanol)

Mp: 161-164°C Form: hydrochloride

Compound of Example 225





Crystal form: yellow powdery (recrystallized from acetone)

Mp: 114-115°C Form: hydrochloride

Example 352

[0105] In 10 ml of dimethylformamide were suspended 1 g of 2-(3,4-diethoxyphenyl)-4-(4-hydroxy-3-methoxycarbonylphenyl)thiazole and 0.35 g of potassium carbonate. The suspension was stirred at room temperature for 30 minutes. Thereto was added 0.46 g of methyl bromoacetate. The mixture was stirred at the same temperature for 4 hours. The solvent was removed by distillation. The residue was extracted with 40 ml of dichloromethane. The extract was washed with 10 ml of water and 10 ml of a saturated aqueous sodium chloride solution, dried over magnesium sulfate, and subjected to distillation to remove the solvent. The residue was recrystallized from diisopropyl ether to obtain 1.1 g of 2-(3,4-diethoxyphenyl)-4-(4-methoxycarbonylmethoxy-3-methoxycarbonylphenyl)thiazole.

Colorless acicular crystals
M.p.: 96-97°C

[0106] In the same procedure as in Example 352 were obtained the compounds of Examples 221 and 225 by using respective starting materials.

Example 365

[0107] 1.2 g of ethyl iodide and 1.5 g of potassium carbonate were added to a solution of 1.2 g of 2-(3-methoxycarbonyl-4-hydroxyphenyl)-4-(3,4-dihydroxyphenyl)thiazole in 20 ml of dimethylformamide. The mixture was stirred at room temperature for 14 hours. The solvent was removed by distillation. The residue was mixed with 40 ml of chloroform and 40 ml of water. The mixture was made acidic with 10% hydrochloric acid and phase separation was conducted. The organic layer was washed with 20 ml f a saturated aqueous sodium chloride solution, dried and subjected to distillation to remove the solvent. The residue was purified by silica gel column chromatography (eluent: dichloromethane/n-hexane = 3/1) to obtain 400 mg of 2-(3-methoxycarbonyl-4-hydroxyphenyl)-4-(3,4-diethoxyphenyl)thiazole.

NMR ($CDC\ell_3$) δ :
1.35-1.60 (6H, m), 3.94 (3H, s), 4.10-4.30 (4H, m), 5.73 (1H, s), 6.90 (1H, d, J=8.3Hz), 7.03 (1H, d,

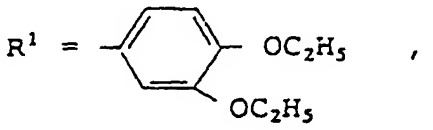
J=8.8Hz), 7.30 (1H, s), 7.48-7.65 (2H, m), 8.13 (1H, dd, J=2.3Hz, 8.8Hz), 8.41 (1H, d, J=2.3Hz)

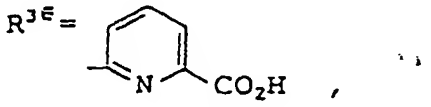
[0108] In the same procedure as in Example 365 were obtained the compounds of Examples 221 and 225 by using respective starting materials.

Examples 371 and 374

[0109] The compounds of Examples 371 and 374 were obtained in the same procedures as in Example 1 and Example 138, by using respective starting materials.

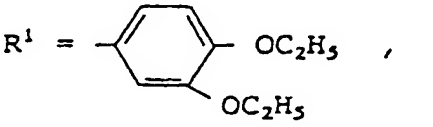
Compound of Example 371

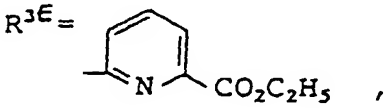




Crystal form: white powdery (recrystallized from ethanol)
M.p.: 182-184°C Form: free

Compound of Example 374





Form: free
NMR: 57)

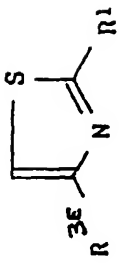
57) NMR ($CDC\ell_3$) δ :
1.41-1.54 (9H, m), 4.07-4.26 (6H, m), 6.92 (1H, d, J=8.4Hz), 7.49 (1H, dd, J=2.0Hz, 8.4Hz), 7.63 (1H, d, J=2.0Hz), 7.86-8.05 (2H, m), 8.20 (1H, s), 8.44 (1H, dd, J-1.0Hz, 7.7Hz)

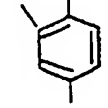
Example 375

[0110] The compound of 371 was obtained in the same procedure as in Example 147, by using respective starting materials.

[0111] The compounds of Examples 387, 390-392, 397-402, 414, 420 and 436-441 shown in Table 13 were obtained by the same procedures as in Example 1 and Example 138, by using respective starting materials.

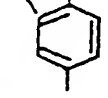
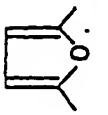
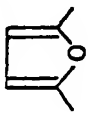
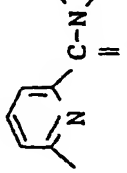
Table 13



Example No.	R^1	R^{3E}	Crystal form (recrystallization solvent)	M.p. (°C) (salt form)
307			Dark yellow acicular (acetone)	213-214 (I)

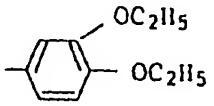
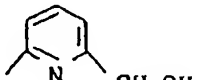
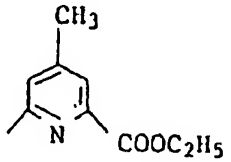
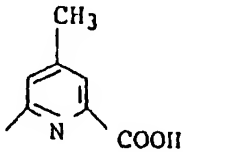
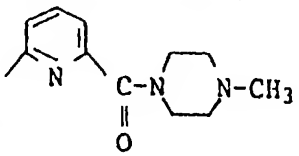
- Cont'd -

Table 13 (Cont'd)

390			White powder (ethanol)	126.8-128.8 (-)
391	"		White powder (ethyl acetate)	206.8-208.6 (-)
392	"		White acicular (n-hexane-ethyl acetate-dichloro-methane)	163.2-164.1 (-)

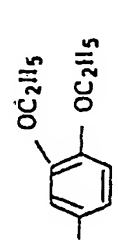
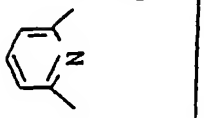
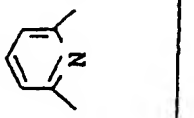
- Cont'd -

Table 13 (Cont'd)

397			White acicular (ethyl acetate-n-hexane)	109-113 (-)
398	"		Yellow powder (ethanol)	181.8-182.4 (decomposed) (-)
399	"		White acicular (ethyl acetate)	180.8-182.2 (-)
400	"		Yellow amorphous	242.5 (decomposed) (4 HCl)

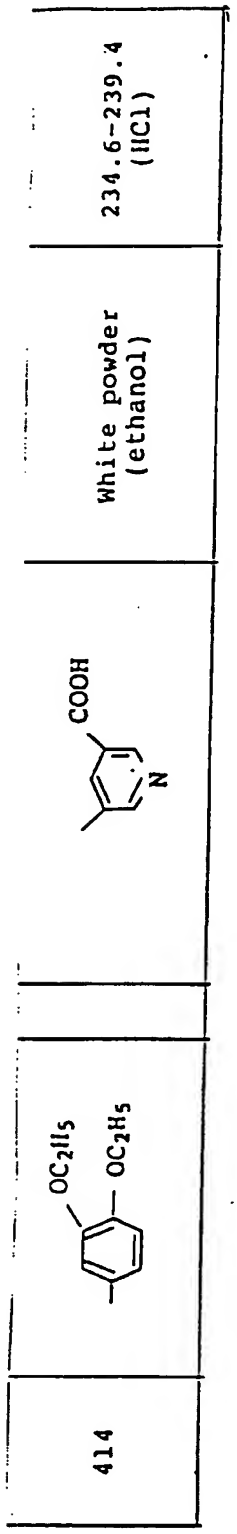
- Cont'd -

Table 13 (Cont'd)

401			White acicular (diethyl ether-n-hexane)	216-217 (-)
402	"		Yellow powder (diethyl ether-ethanol)	195 (decomposed) (2 HCl)

- Cont'd -

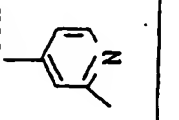
Table 13 (Cont'd)



414	OC_2H_5 OC_2H_5		White powder (ethanol)	234.6-239.4 (HCl)

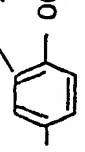
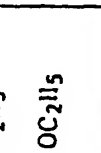
- Cont'd -

Table 13 (Cont'd)

420	OC_2H_5 OC_2H_5		White powder (ethyl acetate)	236.2-237.2 (-)

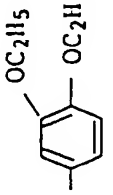
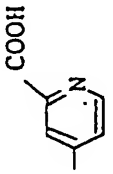
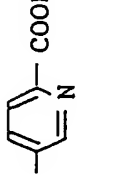
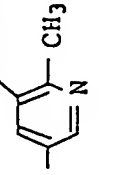
- Cont'd -

Table 13 (Cont'd)

436			Light orange prismatic (ethyl acetate)	230.4-231.4 (-)

- Cont'd -

Table 13 (Cont'd)

437			Dark yellow prismatic (ethyl acetate-diethyl ether-n-hexane)	11 164.6-165.5 (-)
438	"		Light brown powder (ethyl acetate)	153.8-155.4 (-)
439	"		White powder (ethyl acetate)	178-178.6 (-)
440	"		Light yellow powder (ethanol-diethyl ether)	220.8-223.4

- Cont'd -

Table 13 (Cont'd)

441			Brown powder (ethanol)	174.4-175.6 (-)

Example 454

[0112] 200 mg of lithium aluminum hydride was added, at 0°C, to a solution of 1.92 g of 2-(3,4-diethoxyphenyl)-4-(2-ethoxycarbonyl-6-pyridyl)thiazole in 150 ml of tetrahydrofuran. The mixture was stirred in an argon atmosphere for 2 hours. The reaction mixture was mixed with 1 ml of a saturated sodium sulfate slution. The resulting mixture was stirred at 0°C for 30 minutes and filtered through Celite. The filtrate was concentrated. The residue was purified by silica gel column chromatography and recrystallized from ethyl acetate-n-hexane to obtain 360 mg of 2-(3,4-diethoxyphenyl)-4-(2-hydroxymethyl-6-pyridyl)thiazole.

White acicular
M.p.: 109-113°C

Example 455

[0113] 1.13 ml of triethylamine was dropwise added, at room temperature, to a solution of 1 g of 2-(3,4-diethoxyphenyl)-4-(2-carboxy-6-pyridyl)thiazole, 245 mg of dimethylamine hydrochloride and 515 mg of diethyl cyanophosphate in 15 ml of dimethylformamide. The mixture was stirred at the same temperature for 3 hours. The reaction mixture was mixed with 20 ml of water. The resulting mixture was extracted with 50 ml of dichloromethane three times. The dichloromethane layer was dried over sodium sulfate and concentrated. The residue was recrystallized from n-hexane-ethyl acetatedichloromethane to obtain 800 mg of 2-(3,4-diethoxyphenyl)-4-(2-dimethylaminocarbonyl-6-pyrdyl)thiazole.

White acicular
M.p.: 163.2-164.1°C

[0114] The compounds of Examples 400 and 401 were obtained in the same procedure as in Example 455, using respective starting materials.

Example 456

[0115] 730 Milligrams of 2-(3,4-diethoxyphenyl)-4-(2-dimethylaminocarbonyl-6-pyridyl)thiazole was dissolved in 15 ml of tetrahydrofuran at room temperature, then this solution was dropwise added to a suspension of 70 mg of lithium aluminum hydride in 10 ml of diethyl ether, in an argon atmosphere so as to refluxing the reaction mixture. After the completion of the dropwise addition, refluxing was continued for a further 1 hour and 30 minutes. The reaction mixture was mixed with 50 ml of water. The resulting mixture was extracted with three 50-ml portions of dichloromethane. The dichloromethane layer was concentrated. The residue was purified by silica gel thin-layer chromatography. The resulting ethanol solution was mixed with concentrated hydrochloric acid to obtain a hydrochloride. The hydrochloride was recrystallized from a diethyl ether-ethanol mixed solvent to obtain 60 mg of 2-(3,4-diethoxyphenyl)-4-(2-dimethylaminomethyl-6-pyridyl)-thiazole dihydrochloride as a yellow powder.

M.p.: 195°C (decomposed)

Example 458

[0116] In 5 ml of dimethylformamide was dissolved 600 mg of 2-(3,4-diethoxyphenyl)-4-(3-carboxy-4-methoxymethoxyphenyl)thiazole. Thereto was added 56 mg of sodium hydride and 290 mg of 1-bromononane. The mixture was stirred at room temperature for 14 hours. The solvent was removed by distillation. To the residue were added 80 ml of dichloromethane and 30 ml of a 10% aqueous sodium hydroxide solution, and phase separation was conducted. The dichloromethane portion was washed with 20 ml of a saturated aqueous sodium chloride solution, dried and subjected to distillation to remove the solvent. The residue was subjected to silica gel column chromatography. There was obtained, from the dichloromethane layer, 340 mg of 2-(3,4-diethoxyphenyl)-4-(3-nonyloxycarbonyl-4-methoxymethoxyphenyl)thiazole as a colorless oily substance.

Properties: NMR[61)]

1H-NMR ($CDCl_3$) δ :
0.08-1.00 (3H, m), 1.00-1.67 (18H, m), 1.67-1.95 (2H, m), 3.54 (3H, s), 4.16 (2H, q, J=7.0Hz), 4.23 (2H, q, J=7.0Hz), 4.35 (2H, t, J=6.6Hz), 5.30 (2H, s), 6.92 (1H, d, J=8.4Hz), 7.27 (1H, d, J=8.7Hz), 7.36 (1H, s), 7.53 (1H, dd, J=2.0Hz, 8.4Hz), 7.62 (1H, d, J=2.0Hz), 8.08 (1H, dd, J=2.3Hz, 8.7Hz), 8.35 (1H, J=2.3Hz).

[0117] In the same procedure as in Example 458 was obtained the compound of Example 390 by using respective starting materials.

Example 464

[0118] In 15 ml of ethanol was dissolved 220 mg of 2-(3,4- diethoxyphenyl)-4-(3-methoxymethoxycarbonyl-4-methoxymethoxy-5-acetylmethylphenyl)thiazole. Thereto was added 1 ml of 10% hydrochloric acid, and the mixture was refluxed for 2 hours with heating. The solvent was removed by distillation. To the residue were added 20 ml of ethyl acetate and 10 ml of water, and phase separation was conducted. The organic layer was washed with 10 ml of a saturated aqueous sodium chloride solution, dried and subjected to distillation to remove the solvent. The residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 99/1 by v/v) and recrystallized from an n-hexane-ethyl acetate mixed solvent to obtain 2-(3,4-diethoxyphenyl)-4-(3-carboxy-4-hydroxy-5-acetylmethyl)thiazole as a white powder.

[0119] In the same procedure as in Example 467 were obtained the compounds of Examples 391, 399 and by using respective starting materials.

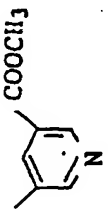
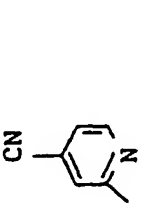
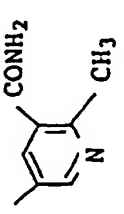
[0120] The compounds of Examples 489, 491-496 and 507-509, shown in Table 14 were obtained in the same procedures as in Example 1 and Example 138, by using respective starting materials.

Table 14

Example No.	R^1	R^3	Crystal form (recrystallization solvent)	M.P. (°C) (salt form)
409	"		Yellow acicular (ethanol)	226.5-229 (-)

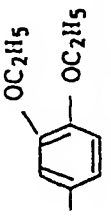
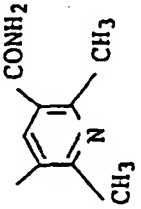
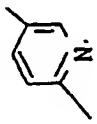
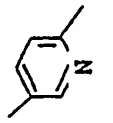
- Cont'd -

Table 14 (Cont'd)

491	〃		Yellow powder (ethanol)	172.4-175.6 (HBr)	
492	〃		Yellow powder (ethanol)	237.2-238 (-)	
493	〃			NMR [7] (-)	

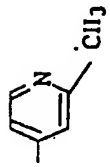
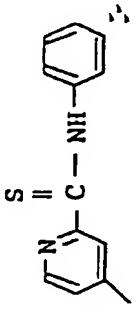
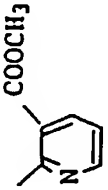
- Cont'd -

Table 14 (Cont'd)

494			Gray powder (ethanol-dimethylformamide)	272-277
495	"		Yellow powder (ethanol)	215-215.8 (-)
496	"		Yellow powder (ethanol)	204-205.4 (HBr)

- Cont'd -

Table 14 (Cont'd)

507	"				NMR 80) (-)
508	"				NMR 81) (-)
509	"				NMR 82) (HBr)

Example 510

[0121] In 30 ml of methanol was dissolved 500 mg of 2-(3,4-diethoxyphenyl)-4-(3-methoxycarbonyl-4-methoxymethoxy-5-formylphenyl)thiazole. Thereto was added 3 ml of a 30% methylamine solution. The mixture was stirred at room temperature for 14 hours and at 70°C for 1 hour. Thereto was added 530 ml of sodium boron hydride with stirring under ice- cooling. The mixture was stirred at room temperature for 3 hours. The solvent was removed from the reaction mixture by distillation. The residue was mixed with 40 ml of ethyl acetate and 20 ml of water, and phase separation was conducted. The organic layer was washed with 10 ml of a saturated aqueous sodium chloride solution, dried and subjected to distillation to remove the solvent. The residue was subjected to silica gel chromatography (eluent: dichloromethane/methanol = 49/1 by v/v). From the eluate was obtained 150 mg of 2-(3,4-diethoxyphenyl)-4-(3-methoxycarbonyl-4-methoxymethoxy-5-methylaminomethylphenyl)thiazole.

Colorless oily
Properties: NMR[73])
^{1}H-NMR ($CDCl_3$) δ:
1.49 (1H, t, J=7.0Hz), 1.51 (3H, t, J=7.0Hz), 2.50 (3H, s), 3.60 (3H, s), 3.92 (2H, s), 3.94 (3H, s), 4.15 (2H, q, J=7.0Hz), 4.22 (2H, q, J=7.0Hz), 5.12 (2H, s), 6.92 (1H, d, J=8.4Hz), 7.44 (1H, s), 7.54 (1H, dd, J=2.1Hz, 8.4Hz), 7.60 (1H, d, J=2.1Hz), 8.13 (1H, d, J=2.4Hz), 8.37 (1H, d, J=2.4Hz).

[0122] The compound of Example 402 was obtained in the same procedure as in Example 510, using starting materials.

Example 511

[0123] In 20 ml of methanol was suspended 300 mg of 2-(3,4- diethoxyphenyl)-4-(3-methoxycarbonyl-4-hydroxy-5-formylphenyl)thiazole with stirring. Threto was added 26.5 mg of sodium boron hydride at 0°C. The mixture was stirred at room temperature for 1 hour. 28.5 mg of sodium boron hydride was further added, and the resulting mixture was stirred at the same temperature for 1 hour. The solvent was removed from the reaction mixture by distillation. To the residue were added 30 ml of dichloromethane and 15 ml of water, and phase separation was conducted. The organic layer was washed with 10 ml of a saturated aqueous sodium chloride solution, dried and subjected to distillation to remove the solvent to obtain 300 mg of 2-(3,4-diethoxyphenyl)-4-(3-methoxycarbonyl-4-hydroxy-5-hydroxymethylphenyl)-thiazole.

Yellow solid
Properties: NMR[74])
^{1}H-NMR ($CDCl_3$) δ:
1.50 (3H, t, J=7.0Hz), 1.52 (3H, t, J=7.0Hz), 2.41 (1H, t, J=6.6Hz), 4.01 (3H, s), 4.16 (2H, q, J=7.0Hz), 4.23 (2H, q, J=7.0Hz), 4.82 (2H, d, J=6.6Hz), 6.93 (1H, d, J=8.4Hz), 7.34 (1H, s), 7.55 (1H, dd, J=2.0Hz, 8.4Hz), 7.60 (1H, d, J=2.0Hz), 8.10 (1H, d, J=2.3Hz), 8.40 (1H, d, J=2.3Hz), 11.38 (1H, s).

[0124] The compounds of Example 397 was obtained in the same procedure as in Example 511, by using respective starting materials.

Example 516

[0125] A mixture of 500 mg of 2-(3,4-diethoxyphenyl)-4-(4-cyano-pyridyl)thiazole, 20 ml of ethanol and 17 ml of a 4% aqueous sodium hydroxide solution was refluxed for 16 hours with heating. The reaction mixture was allowed to stand. Then, 200 ml of water was added thereto. The mixture was extracted with 80 ml of dichromethane two times. The aqueous layer was made acidic (pH = about 3) with concentrated hydrochloric acid and extracted with 150 ml of ethyl acetate three times. The ethyl acetate layer was dried over anhydrous sodium sulfate and concentrated. The residue was recrystallized from ethyl acetate to obtain 290 mg of 2-(3,4-diethoxyphenyl)-4-(4-carboxy-2-pyridyl)thiazole.

White acicular crystals
M.p.: 236.2-237.2°C

Example 518

[0126] 548 mg of lithium aluminum hydride was added to a solution of 5.43 g of 2-(3,4-diethoxyphenyl)-4-(3-methox-

ycarbonyl-4-tert-butyldimethylsilyloxyphenyl)-thiazole in 100 ml of tetrahydrofuran, with ice-cooling. The mixture was stirred at the same temperature for 7 hours. To the reaction mixture were added 1.1 ml of water and 3 g of sodium sulfate. The resulting mixture was filtered through Celite. The filtrate was subjected to distillation to remove the solvent. To the residue were added 200 ml of ethyl acetate and 50 ml of water. The mixture was neutralized with 5 N hydrochloric acid. The insoluble was removed by filtration. The filtrate was subjected to phase separation. The organic layer was washed with 50 ml of water, dried over anhydrous magnesium sulfate and subjected to distillation to remove the solvent. The residue was purified by silica gel column chromatography (eluent: n-hexane/ethyl acetate = 10/1 by v/v) and recrystallized from ethyl acetate-n-hexane to obtain 1.23 g of 2-(3,4-diethoxyphenyl)-4-(3-hydroxymethyl-4-tert-butyldimethylsilyloxyphenyl)thiazole.

White prismatic crystals
M.p.: 101.3-103°C

[0127] The compound of Example 397 was obtained in the same procedure as in Example 518, by using respective starting materials.

Example 520

[0128] The following compounds were obtained in the same procedures as in Examples 1 and 138, by using respective starting materials.

[0129] 4-[2-(3,4-Diethoxyphenyl)-4-thiazolyl]-pyridinium-1-oxide

Properties: ^{1}H-NMR (DMSO-d_6) δ:
1.35 (3H, t, J=6.9Hz), 1.37 (3H, t, J=6.9Hz), 4.07 (4H, m), 7.07 (1H, d, J=8.3Hz), 7.52 (1H, dd, J=2.0Hz, 8.3Hz), 7.58 (1H, d, J=2.0Hz), 8.03 (2H, d, J=7.2Hz), 8.29 (2H, d, J=7.2Hz), 8.33 (1H, s).
2-(3,4-Diethoxyphenyl)-4-(2-cyano-4-pyridinium)thiazole
Properties: ^{1}H-NMR (DMSO-d_6) δ:
1.36 (3H, t, J=6.9Hz), 1.38 (3H, t, J=6.9Hz), 4.08-4.23 (4H, m), 7.08 (1H, d, J=8.3Hz), 7.55-7.61 (2H, m), 8.32 (1H, dd, J=1.3Hz, 5.2Hz), 8.64 (2H, s), 8.84 (1H, d, J=5.2Hz).

Example 521

[0130] The following compounds were obtained in the same procedures as in Examples 1 and 147, by using respective starting materials.

[0131] 4-Ethoxycarbonyl-2-(α-bromoacetyl)furan and 3,4-diethoxythiobenzamide were subjected to the same reaction as in Example 1 and then to the same hydrolysis as in Example 147 to obtain 2-(3,4-diethoxyphenyl)-4-(4-carboxy-2-furyl)thiazole.

[0132] 5-Ethoxycarbonyl-3-(α-bromoacetyl)furan and 3,4-diethoxythiobenzamide were subjected to the same reaction as in Example 1 and then to the same hydrolysis as in Example 147 to obtain 2-(3,4-diethoxyphenyl)-4-(5-carboxy-3-furyl) thiazole.

Pharmacological Tests

[0133] The pharmacological tests for present compounds were conducted according to the following methods.

(1) Activity for inhibiting the generation of superoxide radical (O_2^-) in human neutrophilic leukocytes

[0134] Human neutrophilic leukocytes were prepared in accordance with the method of M. Markert et al. (Methods in Enzymology, vol. 105; pp. 358-365, 1984). That is, a whole blood obtained from a healthy adult and treated by anticoagulation method was subjected to a dextran-hypotonic treatment to obtain leukocyte cells. The leukocyte cells were then subjected to a density gradient ultacentrifugation by Ficoll-Paque to obtain a neutrophilic leukocyte fraction.

[0135] O_2^- generation was examined by the ferricytochrome C method in accordance with the method of B.N. Cronstein et al. (Journal of Experimental Medicine, vol. 158, pp. 1160-1177 (1983)]. That is, $1x10^{-6}$ cell of neutrophilic leukocytes were stimulated with $3x10^{-7}$M of N-formyl-L-methionyl-L-leucyl-L-phenylalanine (FMLP) at 37°C in the presence of 1.3 mg/ml of ferricytochrome C and 5 μg/ml of cytochalasin B in a Hepes-buffered Hank's solution (pH 7.4); the amount of ferrocytochrome C formed by 4 minutes of reduction was determined by measuing an absorbance at a wavelength of 550 nm using a spectrophotometer; an absorbance in the presence of 25.1 μg/ml of superoxide dismutase (SOD) was also measured; the difference of the two absorbances was taken as the amount of superoxide rad-

ical (O_2^-) generated. Each test compound was dissolved in dimethyl sulfoxide (DMSO); the solution was added to neutrophilic leukocytes before the addition of FMLP; then, the neutrophilic leukocytes were pre-incubated at 37°C. By using the amount of superoxide radical (O_2^-) generated when the test compound solution was added and the amount or superoxide radical (O_2^-) generated when only the solvent (DMSO) was added, a ratio of inhibition (%) was calculated, and the activity for inhibiting superoxide radical (O_2^-) generation was expressed as 50% inhibitory concentration (IC_{50}).

Test compounds

[0136]

60. 2-(3,4-Dimethoxyphenyl)-4-(2-pyridyl)thiazole hydrochloride
115. 4-(6-Carboxy-2-pyridyl)-2-(3,4-diethoxyphenyl)-thiazole
121. 2-(3,4-Diethoxyphenyl)-4-(2-methoxycarbonyl-5-furyl)thiazole
122. 2-(3,4-Diethoxyphenyl)-4-(2-carboxy-5-furyl)-thiazole
123. 2-(3,4-Diethoxyphenyl)-4-(2-dimethylaminocarbonyl-6-pyridyl)thiazole
128. 2-(3,4-Diethoxyphenyl)-4-[2-(4-methyl-1-piperazinyl)carbonyl)-6-pyridyl]thiazole
135. 2-(3,4-Diethoxyphenyl)-4-(3-carboxy-5-pyridyl)-thiazole hydrochloride
141. 2-(3,4-Diethoxyphenyl)-4-(2-methyl-3-carboxy-5-pyridyl)thiazole
143. 2-(3,4-Diethoxyphenyl)-4-(3-carboxy-6-pyridyl)-thiazole
144. 2-(3,4-Diethoxyphenyl)-4-(2-carboxy-5-pyridyl)-thiazole

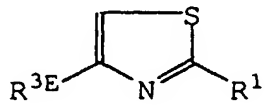
[0137] The results are shown in Table 15.

Table 15

Test compound (No.)	IC_{50} (μM)	Test compound (No.)	IC_{50} (μM)
60	0.05	128	0.58
115	0.08	135	0.035
121	0.038	141	0.094
122	0.019	143	0.27
123	0.38	144	0.035

Claims

1. A thiazole derivative of the general formula (1),

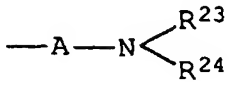


(1)

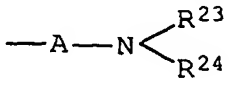
wherein:

R^1 represents a phenyl group which may have 1-3 alkoxy groups as substituents; and

R^{3E} represents either (i) a pyridyl group optionally substituted by 1 to 3 substituents selected from an alkyl group, a benzoyl group, a C_1-C_6 alkanoyl group, a hydroxy group, a carboxy group, a C_1-C_6 alkoxycarbonyl group, a C_1-C_6 alkylthio group, a group of the formula:



(wherein A is a C_1-C_6 alkylene group or a group -C(=O)-; and R^{23} and R^{24}, which may be the same or different, each represent a hydrogen atom or a C_1-C_6 alkyl group; further R^{23} and R^{24} as well as the adjacent nitrogen atom being bonded thereto, together with or without another nitrogen atom or oxygen atom may form a five- to six-membered saturated heterocyclic group; and said five- to six-membered heterocyclic group may have a C_1-C_6 alkyl group as a substituent), a cyano group, a C_1-C_6 alkyl group having hydroxy groups, a phenylaminothiocarbonyl group and an amino C_1-C_6 alkoxycarbonyl group which may have a C_1-C_6 alkyl group as a substituent; or (ii) a furyl group which has 1 to 3 substituents selected from an alkyl group, a benzoyl group, a C_1-C_6 alkanoyl group, a hydroxy group, a carboxy group, a C_1-C_6 alkoxycarbonyl group, a C_1-C_6 alkylthio group, a group of the formula :



(wherein A, R^{23} and R^{24} are as defined above); a cyano group, a C_1-C_6 alkyl group having hydroxy groups, a phenylaminothiocarbonyl group and an amino C_1-C_6 alkoxycarbonyl group which may have a C_1-C_6 alkyl group as a substituent,

or a salt thereof.

2. A thiazole derivative according to Claim 1, wherein R^{3E} is a pyridyl group which may have 1 to 3 substituents selected from the group consisting of a carboxy group, a hydroxy group, a C_1-C_6 alkoxycarbonyl group and a C_1-C_6 alkyl group having hydroxy groups; or a salt thereof.

3. A thiazole derivative according to Claim 1, wherein R^{3E} is a furyl group which has 1 to 3 substituents selected from the group consisting of a carboxy group, a hydroxy group, a C_1-C_6 alkoxycarbonyl group and a C_1-C_6 alkyl group having hydroxy groups; or a salt thereof.

4. A thiazole derivative according to Claim 2, wherein R^{3E} is a pyridyl group which may have 1 to 3 substituents selected from the group consisting of a carboxy group, and a C_1-C_6 alkoxycarbonyl group; or a salt thereof.

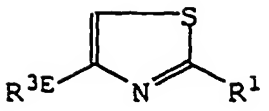
5. 2-(3,4-Diethoxyphenyl)-4-(2-carboxy-6-pyridyl)-thiazole.

6. A superoxide radical inhibitor comprising as the active ingredient a thiazole derivative or a salt thereof of Claim 1 and a pharmaceutically acceptable carrier.

7. A superoxide radical inhibitor comprising as the active ingredient 2-(3,4-Diethoxyphenyl)-4-(2-carboxy-6-pyridyl) thiazole and a pharmaceutically acceptable carrier.

8. The use of a thiazole derivative according to any of Claims 1-5 for the manufacture of a medicament for the treatment of ulcers of the digestive tract, ischemic heart disease, cerebrovascular disease, hepatic and renal function improver for disturbances caused by transplant or microcirculation failure, Bechet disease, dermatovascular inflammation, ulcerative colitis, malignant rheumatoid, arthritis, artheriosclerosis or diabetes mellitus, or for use as a hepatic or renal function improver.

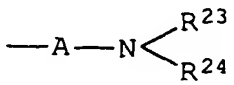
9. A process for producing a thiazole derivative represented by the general formula



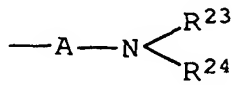
(1)

wherein:

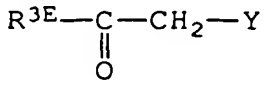
R^1 represents a phenyl group which may have 1-3 alkoxy groups as substituents; and
R^{3E} represents either (i) a pyridyl group optionally substituted by 1 to 3 substituents selected from an alkyl group, a benzoyl group, a C_1-C_6 alkanoyl group, a hydroxy group, a carboxy group, a C_1-C_6 alkoxycarbonyl group, a C_1-C_6 alkylthio group, and a group of the formula :



(wherein A is a C_1-C_6 alkylene group or a group -C(=O)-; and R^{23} and R^{24}, which may be the same or different, each represent a hydrogen atom or a C_1-C_6 alkyl group; further R^{23} and R^{24} as well as the adjacent nitrogen atom being bonded thereto, together with or without another nitrogen atom or oxygen atom may form a five- to six-membered saturated heterocyclic group; and said five- to six-membered heterocyclic group may have a C_1-C_6 alkyl group as a substituent), a cyano group, a C_1-C_6 alkyl group having hydroxy group, a phenylaminothiocarbonyl group and an amino C_1-C_6 alkoxycarbonyl group which may have a C_1-C_6 alkyl group as a substituent) ; or (ii) a furyl group which has 1 to 3 substituents selected from an alkyl group, a benzoyl group, a C_1-C_6 alkanoyl group, a hydroxy group, a carboxy group, a C_1-C_6 alkoxycarbonyl group, a C_1-C_6 alkylthio group, and a group of the formula:

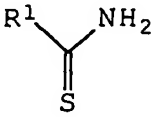


(wherein A, R^{23} and R^{24} are as defined above) or a salt thereof,
which process comprises the step of reacting a compound of formula (2),



(2)

(wherein R^{3E} is the same as defined above, and Y represents a halogen atom) with a compound of formula (3),

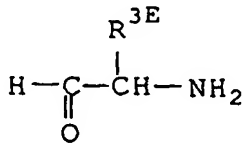


(3)

(wherein R^1 is the same as defined above) in an appropriate solvent with heating.

10. A process for producing a thiazole derivative of the general formula (1) as defined in Claim 9 or a salt thereof,

which comprises the step of reacting a compound of formula (6),

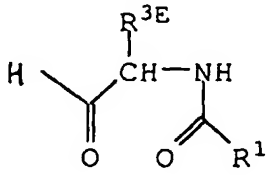


(6)

(wherein R^{3E} is as defined in Claim 9) with a compound represented by the general formula (4),

$$R^1\text{-COOH} \qquad (4)$$

(wherein R^1 is as defined in Claim 9) to produce a compound of formula (7),

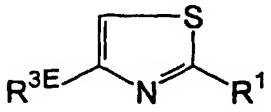


(7)

and then reacting the compound (7) in a solvent-free state or in an appropriate solvent in the presence of a sulfurizing agent.

Patentansprüche

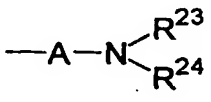
1. Thiazolderivat der allgemeinen Formel (1)



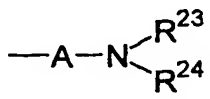
(1)

worin R^1 eine Phenylgruppe repräsentiert, die 1 bis 3 Alkoxygruppen als Substituenten aufweisen kann, und

R^{3E} repräsentiert entweder (i) eine Pyridylgruppe, die wahlweise mit 1 bis 3 Substituenten substituiert ist, ausgewählt aus einer Alkylgruppe, einer Benzoylgruppe, einer $C_{1\text{-}6}$-Alkanoylgruppe, einer Hydroxygruppe, einer Carboxygruppe, einer $C_{1\text{-}6}$-Alkoxycarbonylgruppe, einer $C_{1\text{-}6}$-Alkylthiogruppe, einer Gruppe der Formel



(worin A eine C_{1-6}-Alkylengruppe oder eine -C(=O) -Gruppe ist; und R^{23} und R^{24}, die gleich oder verschieden sein können, repräsentieren ein Wasserstoffatom oder eine C_{1-6}-Alkylgruppe; darüber hinaus können R^{23} und R^{24} sowie das daran gebundene benachbarte Stickstoffatom zusammen mit einem oder ohne ein weiteres Stickstoffatom oder Sauerstoffatom eine 5- oder 6-gliedrige gesättigte, heterocyclische Gruppe bilden, und diese 5- bis 6-gliedrige heterocyclische Gruppe kann eine C_{1-6}-Alkylgruppe als Substituenten aufweisen), einer Cyanogruppe, einer C_{1-6}-Alkylgruppe mit Hydroxygruppen, einer Phenylaminothiocarbonylgruppe und einer Amino-C_{1-6}-alkoxycarbonylgruppe, die eine C_{1-6}-Alkylgruppe als Substituenten aufweisen kann; oder (ii) eine Furylgruppe mit 1 bis 3 Substituenten, ausgewählt aus einer Alkylgruppe, einer Benzoylgruppe, einer C_{1-6}-Alkanoylgruppe, einer Hydroxygruppe, einer Carboxygruppe, einer C_{1-6}-Alkoxycarbonylgruppe, einer C_{1-6}-Alkylthiogruppe, einer Gruppe der Formel



(worin A, R^{23} und R^{24} wie oben definiert sind); einer Cyanogruppe, einer C_{1-6}-Alkylgruppe mit Hydroxygruppen, einer Phenylaminothiocarbonylgruppe und einer Amino-C_{1-6}-alkoxycarbonylgruppe, die eine C_{1-6}-Alkylgruppe als Substituenten aufweisen kann,

oder ein Salz hiervon.

2. Thiazolderivat gemäss Anspruch 1, worin R^{3E} eine Pyridylgruppe ist, die 1 bis 3 Substituenten aufweisen kann, ausgewählt aus einer Carboxygruppe, einer Hydroxygruppe, einer C_{1-6}-Alkoxycarbonylgruppe und einer C_{1-6}-Alkylgruppe mit Hydroxygruppen; oder ein Salz davon.

3. Thiazolderivat gemäss Anspruch 1, worin R^{3E} eine Furylgruppe ist, die 1 bis 3 Substituenten aufweist, ausgewählt aus einer Carboxygruppe, einer Hydroxygruppe, einer C_{1-6}-Alkoxycarbonylgruppe und einer C_{1-6}-Alkylgruppe mit Hydroxygruppen; oder ein Salz davon.

4. Thiazolderivat gemäss Anspruch 2, worin R^{3E} eine Pyridylgruppe ist, die 1 bis 3 Substituenten aufweist, ausgewählt aus einer Carboxygruppe und einer C_{1-6}-Alkoxycarbonylgruppe; oder ein Salz davon.

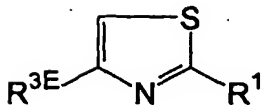
5. 2-(3,4-Diethoxyphenyl)-4-(2-carboxy-6-pyridyl)-thiazol.

6. Superoxidradikalinhibitor, der als aktiven Bestandteil ein Thiazolderivat oder ein Salz davon gemäss Anspruch 1 und einen pharmazeutisch annehmbaren Träger umfasst.

7. Superoxidradikalinhibitor, der als aktiven Bestandteil 2-(3,4-Diethoxyphenyl)-4-(2-carboxy-6-pyridyl)thiazol und einen pharmazeutisch annehmbaren Träger umfasst.

8. Verwendung eines Thiazolderivats gemäss mindestens einem der Ansprüche 1 bis 5 zur Herstellung eines Medikaments zur Behandlung von Geschwüren des Verdauungstrakts, ischämischer Herzerkrankungen, cerebrovaskulärer Erkrankungen, zur Verbesserung der hepatischen und renalen Funktionen bei Störungen, die durch Transplantations- oder Mikrozirkulationsversagen hervorgerufen werden, zur Behandlung der Bechet-Erkrankung, dermatovaskulärer Entzündung, ulcerativer Colitis, maligner rheumatoider Arthritis, Arteriosklerose oder Diabetis mellitus oder zur Verwendung als Verbesserer der hepatischen oder renalen Funktion.

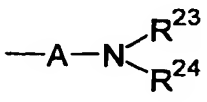
9. Verfahren zur Herstellung eines Thiazolderivats der allgemeinen Formel



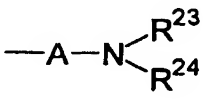
(1)

worin R^1 eine Phenylgruppe repräsentiert, die 1 bis 3 Alkoxygruppen als Substituenten aufweisen kann, und

R^{3E} repräsentiert entweder (i) eine Pyridylgruppe, die wahlweise mit 1 bis 3 Substituenten substituiert ist, ausgewählt aus einer Alkylgruppe, einer Benzoylgruppe, einer C_{1-6}-Alkanoylgruppe, einer Hydroxygruppe, einer Carboxygruppe, einer C_{1-6}-Alkoxycarbonylgruppe, einer C_{1-6}-Alkylthiogruppe, einer Gruppe der Formel

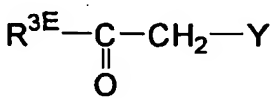


(worin A eine C_{1-6}-Alkylengruppe oder eine -C(=O)-Gruppe ist; und R^{23} und R^{24}, die gleich oder verschieden sein können, repräsentieren ein Wasserstoffatom oder eine C_{1-6}-Alkylgruppe; darüber hinaus können R^{23} und R^{24} sowie das daran gebundene benachbarte Stickstoffatom zusammen mit einem oder ohne ein weiteres Stickstoffatom oder Sauerstoffatom eine 5- oder 6-gliedrige gesättigte, heterocyclische Gruppe bilden, und diese 5- bis 6-gliedrige heterocyclische Gruppe kann eine C_{1-6}-Alkylgruppe als Substituenten aufweisen), einer Cyanogruppe, einer C_{1-6}-Alkylgruppe mit Hydroxygruppen, einer Phenylaminothiocarbonylgruppe und einer Amino-C_{1-6}-alkoxycarbonylgruppe, die eine C_{1-6}-Alkylgruppe als Substituenten aufweisen kann; oder (ii) eine Furylgruppe mit 1 bis 3 Substituenten, ausgewählt aus einer Alkylgruppe, einer Benzoylgruppe, einer C_{1-6}-Alkanoylgruppe, einer Hydroxygruppe, einer Carboxygruppe, einer C_{1-6}-Alkoxycarbonylgruppe, einer C_{1-6}-Alkylthiogruppe, einer Gruppe der Formel



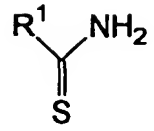
(worin A, R^{23} und R^{24} wie oben definiert sind); oder ein Salz hiervon,

das Verfahren umfasst den Schritt der Umsetzung einer Verbindung der Formel (2) :



(2)

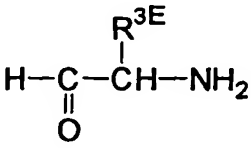
(worin R^{3E} wie oben definiert ist, und Y repräsentiert ein Halogenatom) mit einer Verbindung der Formel (3) :



(3)

(worin R^1 wie oben definiert ist) in einem geeigneten Lösungsmittel unter Erwärmen.

10. Verfahren zur Herstellung eines Thiazolderivats der allgemeinen Formel (1) wie in Anspruch 9 definiert oder eines Salzes davon, umfassend den Schritt der Umsetzung einer Verbindung der Formel (6) :

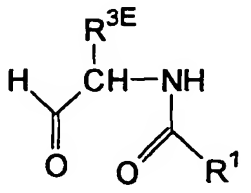


(6)

(worin R^{3E} wie in Anspruch 9 definiert ist) mit einer Verbindung der allgemeinen Formel (4) :

$$R^1—COOH \qquad (4)$$

(worin R^1 wie in Anspruch 9 definiert ist), wodurch eine Verbindung der Formel (7) hergestellt wird:

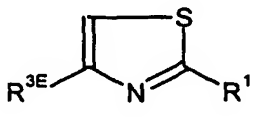


(7)

und anschliessende Umsetzung der Verbindung (7) in einem lösungsmittelfreien Zustand oder in einem geeigneten Lösungsmittel in Gegenwart eines Sulfurierungsmittels.

Revendications

1. Dérivé de thiazole de formule générale (1) :

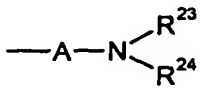


(1)

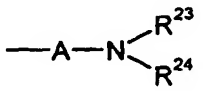
dans laquelle :

R^1 représente un groupe phényle qui peut comporter de 1 à 3 groupes alcoxy à titre de substituants ; et

R^{3E} représente soit (i) un groupe pyridyle éventuellement substitué par 1 à 3 substituants choisis parmi un groupe alkyle, un groupe benzoyle, un groupe alcanoyle en C_1 à C_6, un groupe hydroxy, un groupe carboxy, un groupe alcoxycarbonyle en C_1 à C_6, un groupe alkylthio en C_1 à C_6, un groupe de formule :



(dans laquelle A est un groupe alkylène en C_1 à C_6 ou un groupe -C(=O)- ; et chacun des groupements R^{23} et R^{24}, qui peuvent être identiques ou différents, représente un atome d'hydrogène ou un groupe alkyle en C_1 à C_6 ; en outre R^{23} et R^{24}, ainsi que l'atome d'azote adjacent lié à ceux-ci, peuvent former, avec ou sans un autre atome d'azote ou atome d'oxygène, un groupe hétérocyclique saturé à cinq ou six chaînons ; et ledit groupe hétérocyclique à cinq ou six chaînons peut comporter un groupe alkyle en C_1 à C_6 à titre de substituant), un groupe cyano, un groupe alkyle en C_1 à C_6 comportant des groupements hydroxy, un groupe phénylaminothiocarbonyle et un groupe amino(alcoxycarbonyle en C_1 à C_6) qui peut comporter un groupe alkyle en C_1 à C_6 à titre de substituant ; soit (ii) un groupe furyle qui comporte de 1 à 3 substituants choisis parmi un groupe alkyle, un groupe benzoyle, un groupe alcanoyle en C_1 à C_6, un groupe hydroxy, un groupe carboxy, un groupe alcoxycarbonyle en C_1 à C_6, un groupe alkylthio en C_1 à C_6, un groupe de formule :



(dans laquelle A, R^{23} et R^{24} sont tels que définis ci-dessus) ; un groupe cyano, un groupe alkyle en C_1 à C_6 comportant des groupements hydroxy, un groupe phénylaminothiocarbonyle et un groupe amino(alcoxycarbonyle en C_1 à C_6) qui peut comporter un groupe alkyle en C_1 à C_6 à titre de substituant,
ou un sel d'un tel dérivé.

2. Dérivé de thiazole selon la revendication 1, dans lequel R^{3E} est un groupe pyridyle qui peut comporter de 1 à 3 substituants choisis dans l'ensemble constitué par un groupe carboxy, un groupe hydroxy, un groupe alcoxycarbonyle en C_1 à C_6 et un groupe alkyle en C_1 à C_6 comportant des groupements hydroxy ; ou un sel d'un tel dérivé.

3. Dérivé de thiazole selon la revendication 1, dans lequel R^{3E} est un groupe furyle qui comporte de 1 à 3 substituants choisis dans l'ensemble constitué par un groupe carboxy, un groupe hydroxy, un groupe alcoxycarbonyle en C_1 à C_6 et un groupe alkyle en C_1 à C_6 comportant des groupements hydroxy ; ou un sel d'un tel dérivé.

4. Dérivé de thiazole selon la revendication 2, dans lequel R^{3E} est un groupe pyridyle qui comporte de 1 à 3 substituants choisis dans l'ensemble constitué par un groupe carboxy et un groupe alcoxycarbonyle en C_1 à C_6 ; ou un sel d'un tel dérivé.

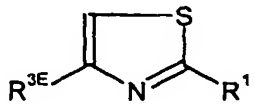
5. 2-(3,4-diéthoxyphényl)-4-(2-carboxy-6-pyridyl)-thiazole.

6. Inhibiteur de radical superoxyde comprenant, à titre d'ingrédient actif, un dérivé de thiazole ou un sel d'un tel dérivé, selon la revendication 1, et un véhicule acceptable en pharmacie.

7. Inhibiteur de radical superoxyde comprenant, à titre d'ingrédient actif, du 2-(3,4-diéthoxyphényl)-4-(2-carboxy-6-pyridyl)thiazole, et un véhicule acceptable en pharmacie.

8. Utilisation d'un dérivé de thiazole selon l'une quelconque des revendications 1 à 5, pour la fabrication d'un médicament destiné au traitement d'ulcères du tube digestif, d'une maladie coronarienne, d'un accident vasculaire cérébral, ou servant d'améliorateur des fonctions hépatique et rénale pour des perturbations provoquées par une transplantation ou une défaillance microcirculatoire, la maladie de Bechet, une inflammation dermatovasculaire, une colite ulcéreuse, un rhumatoïde malin, une arthrite, une artériosclérose ou un diabète sucré, ou pour une utilisation en tant qu'améliorateur de la fonction hépatique ou rénale.

9. Procédé pour produire un dérivé de thiazole représenté par la formule générale :

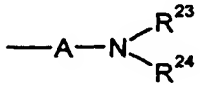


(1)

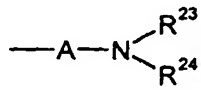
dans laquelle :

R^1 représente un groupe phényle qui peut comporter de 1 à 3 groupes alcoxy à titre de substituants ; et

R^{3E} représente soit (i) un groupe pyridyle éventuellement substitué par 1 à 3 substituants choisis parmi un groupe alkyle, un groupe benzoyle, un groupe alcanoyle en C_1 à C_6, un groupe hydroxy, un groupe carboxy, un groupe alcoxycarbonyle en C_1 à C_6, un groupe alkylthio en C_1 à C_6, et un groupe de formule :



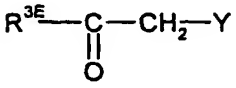
(dans laquelle A est un groupe alkylène en C_1 à C_6 ou un groupe -C(=O)- ; et chacun des groupements R^{23} et R^{24}, qui peuvent être identiques ou différents, représente un atome d'hydrogène ou un groupe alkyle en C_1 à C_6 ; en outre R^{23} et R^{24}, ainsi que l'atome d'azote adjacent lié à ceux-ci, peuvent former, avec ou sans un autre atome d'azote ou atome d'oxygène, un groupe hétérocyclique saturé à cinq ou six chaînons ; et ledit groupe hétérocyclique à cinq ou six chaînons peut comporter un groupe alkyle en C_1 à C_6 à titre de substituant), un groupe cyano, un groupe alkyle en C_1 à C_6 comportant un groupe hydroxy, un groupe phénylaminothiocarbonyle et un groupe amino(alcoxycarbonyle en C_1 à C_6) qui peut comporter un groupement alkyle en C_1 à C_6 à titre de substituant ; soit (ii) un groupe furyle qui comporte de 1 à 3 substituants choisis parmi un groupe alkyle, un groupe benzoyle, un groupe alcanoyle en C_1 à C_6, un groupe hydroxy, un groupe carboxy, un groupe (alcoxycarbonyle en C_1 à C_6), un groupe alkylthio en C_1 à C_6, un groupe de formule :



(dans laquelle A, R^{23} et R^{24} sont tels que définis ci-dessus)

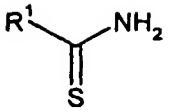
ou un sel d'un tel dérivé,

lequel procédé comprend l'étape consistant à faire réagir un composé de formule (2) :



(2)

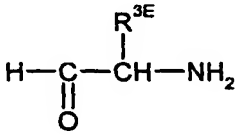
(dans laquelle R^{3E} est tel que défini ci-dessus, et Y représente un atome d'halogène)
avec un composé de formule (3) :



(3)

(dans laquelle R^1 est tel que défini ci-dessus)
dans un solvant approprié, avec chauffage.

10. Procédé pour produire un dérivé de thiazole de formule générale (1) tel que défini dans la revendication 9, ou un de ses sels, qui comprend l'étape consistant à faire réagir un composé de formule (6) :

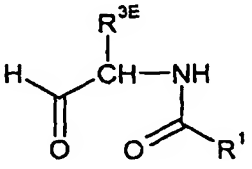


(6)

(dans laquelle R^{3E} est tel que défini dans la revendication 9)
avec un composé représenté par la formule générale (4) :

$$R^1—COOH \qquad (4)$$

(dans laquelle R^1 est tel que défini dans la revendication 9)
pour produire un composé de formule (7) :



(7)

et ensuite à faire réagir le composé (7) dans un état sans solvant ou dans un solvant approprié en présence d'un agent de sulfuration.